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PLASTIC STUDIES IN ABNORMAL RENAL ARCHITECTURE

II. THE MORPHOLOGY OF THE ABNORMAL NEPHRON IN TERMINAL HEMORRHAGIC BRIGHT'S DISEASE

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In the first study of this series two types of the architectural unit from the kidney in the terminal stage of hemorrhagic Bright's disease were presented in plastic three dimensional form by means of models reconstructed by the Born wax plate method.[1] The need of such an objective representation of so complex a morphologic structure as the abnormal renal unit is manifest, but while a casual glance at the complicated pattern of the histologic section shows at once that an infinite variety of modifications of these two simpler types must exist, actual experience with the laborious procedure of model building soon convinces one that a knowledge of their diversity can never be obtained by its time-consuming employment. Fortunately an auxiliary method is at hand, which, though it lacks certain of the advantages of the presentation by models, furnishes us with the ability to study in a relatively short time a large number of units in a three dimensional form that can, if desired, be registered stereoscopically. Not only are the multiform varieties of alteration thus available for consideration, but quantitative studies become possible so that the significance of any particular change can be determined by the frequency of its occurrence. This is the method of maceration and microdissection, the method by which Huber [2] and Peter [3] established in its modern form our knowledge of the architecture of the normal kidney.

TECHNIC

The details of the technical procedure require but a brief description. Pieces of a kidney that had been fixed and preserved in a dilute

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1. Oliver, J., and Lund, E.: Arch. Path. **15**:755, 1933.
2. Huber, G. C.: Am. J. Anat. (supp.) **4**:1, 1904.
3. Peter, K.: Untersuchungen über Bau und Entwicklung der Niere, Jena, Gustav Fischer, 1927.

solution of formaldehyde U. S. P. (1:10) or in Kaiserling's solution [4] were placed in concentrated hydrochloric acid and allowed to stand at room temperature until sufficiently softened. The time required depends on various factors, such as the degree of fibrosis that exists in the tissue, the size of the block under treatment, the length of its fixation, which may be years, and the temperature of the room. In some cases maceration will be sufficient in two days, in others a week is required, but these variations are of little moment, since the process may be watched and stopped at the desired point. We found that fresh tissue is of no definite advantage, though it macerates more rapidly, and since we wished to examine again kidneys that we had been studying for many years by other methods only fixed material was available.

When sufficiently macerated the almost diffluent tissue is washed in repeated changes of distilled water and may be kept for several days. The final procedure is the separation of the individual units from each other under the binocular microscope by dissection with needles. Illumination was obtained by reflected light.

No attempt was made, except in one special case to be mentioned later, to mount and preserve the isolated structures. The slightest pressure, even that developing from surface tension if the object is removed to a shallow drop on a slide, distorts the contours of the delicate tubules. They were therefore studied suspended in the water in which they had been dissected. Camera lucida drawings were made for record and illustration, but as an integral part of the method stereoscopic photomicrographs were taken at a standard magnification of 20. Such stereograms are in many ways preferable for study to the original preparations. Practically no detail is lost in the recording of the unstained structures, and the contours and twists and turns of a distorted tubule are more readily followed when the specimen is fixed on the photographic plate than when it floats suspended in water.

MATERIAL

The kidneys examined were all from cases of terminal hemorrhagic Bright's disease (chronic glomerular nephritis) in a series whose clinical and pathologic features have been previously described.[5] In the present study we are not interested in the topographic morphology of the individual nephritic kidney, but rather in a description of the various abnormal forms which the nephron may assume as a result of the chronic processes concerned. In a later study the combinations that are found in typical examples of the disease will be considered. The details of

4. This solution consists of 30 Gm. of potassium acetate, 10 Gm. of potassium nitrate, 750 cc. of distilled water and 300 cc. of a solution of formaldehyde.

5. Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931.

clinical history and of the general histologic characteristics of the kidney as seen in ordinary sections are therefore not given, but may be obtained if desired for the particular structures that have been illustrated by reference to the descriptions of the plate figures.

For simplification and completeness of description the course of the nephron from the glomerulus to the exit of the terminal ducts of Bellini into the pelvis will be followed, and the variations observed in each constituent portion will be described and compared with the normal.

THE NORMAL NEPHRON

Since a relative change in size is an important feature of the pathologic alterations to be described, the divisions of the human nephron as isolated from the normal kidney of a young adult are illustrated for the purpose of subsequent comparison. In figure 2 an intact complete short loop nephron from the glomerulus to the collecting tubule is shown. For a detailed description of the characteristics of the various segments of the normal unit reference may be made to Peter's monograph.[3]

THE NEPHRON IN TERMINAL HEMORRHAGIC BRIGHT'S DISEASE

The Glomerulus and Its Vessels.—The vessels of the glomeruli of the normal kidney are exceedingly delicate so that only with great difficulty can they be preserved intact with the isolated glomerulus. Their walls are thin and translucent and their contours even and tapering (fig. 1). In the abnormal kidney [6] they may be tremendously thickened, a fact evidenced by the comparative ease with which one obtains sprig-like portions of the terminal artery on which the diseased glomeruli hang in abundance by means of their afferent arterioles (figs. 3 to 7 and 13). The artery appears opaque with fusiform dilatations alternating with angular constrictions (figs. 3, 4, 6 and 13), and areas of fatty change, dazzlingly white, are scattered at random along its course in the form of diffuse mottled patches (figs. 7, 13 and 22).

From such sclerosed arteries spring the afferent arterioles; they too are thickened and rigid and at times flecked with bright patches of fatty change. Irregularity of contour, even aneurysmal-like bulgings are seen (fig. 13). Springing from the arterioles at an obtuse or even a right angle is frequently found Ludwig's vessel, dilated to a caliber equal to that of the parent arteriole (figs. 3, 6, 22 and 28). The significance of the size of this shunt across the occluded capillary bed of the glomerulus and the frequency with which it can be demonstrated will be mentioned later in considering certain of the changes that occur in the tubular apparatus.

6. For the sake of brevity the term "abnormal kidney" is used to denote the kidney in terminal hemorrhagic Bright's disease.

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Fig. 1.—Terminal branches of an interlobular artery from a normal kidney showing glomeruli, to one of which is attached the first part of the proximal convolution. Another shows both an afferent and an efferent vessel; × 15.

Fig. 2.—A complete nephron from a normal kidney. The junction of several other nephrons with the collecting tubule is shown. *A* to *B*, proximal convolution, periglomerular cluster; *B* to *C*, proximal convolution, terminal segment; *C* to *D*, narrow portion of Henle's loop; *D* to *E*, broad portion of Henle's loop; *E* to *F*, distal convolution; *F* to *G*, connecting piece; *G* to *H*, peripheral collecting tubule; × 15.

Fig. 3.—Figures 3 to 61 depict kidneys with terminal hemorrhagic Bright's disease. Figure 3 shows terminal branches of an interlobular artery with glomeruli. Note the irregularity in size and the fat content of the tufts. Ludwig's vessel is apparent in the afferent vessel of the upper glomerulus on the left; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 4.—A similar vessel showing atrophied and enlarged glomeruli; × 15 (Addis and Oliver,[5] case 37, p. 348).

Fig. 5.—Irregularly dilated interlobular artery with fatty degeneration that extends into the afferent vessels; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 6.—Dilated terminal artery showing glomeruli with Ludwig's vessel (middle glomerulus) and a long efferent vessel; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 7.—Terminal artery showing rigid sclerosis and extreme fatty change. The glomerular tuft is also diffusely infiltrated with fat; × 15 (Addis and Oliver,[5] case 15, p. 238).

Fig. 8.—Isolated glomeruli showing various forms of distortion and irregular fatty change in the tufts; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 9.—A glomerulus greatly enlarged with a complete hypertrophied and hyperplastic terminal proximal convolution. The distal convolution, empty and dilated, is shown attached to the side of the glomerulus; × 15 (Addis and Oliver,[5] case 6, p. 197).

Fig. 10.—Complete short loop nephron from glomerulus to collecting tubule. There is a marked hypertrophy and hyperplasia of the proximal convolution. The narrow segment of Henle's loop is a short straight segment; × 15 (Addis and Oliver,[5] 32, p. 325).

Fig. 11.—Markedly hypertrophied and hyperplastic proximal convolution. Note the kinked loops of its terminal portion; × 15 (Addis and Oliver,[5] case 32, p. 325).

Fig. 12.—Another complete hypertrophied and hyperplastic proximal convolution with extreme kinking of terminal segment; × 15 (Addis and Oliver,[5] case 32, p. 325).

The efferent vessel is much more difficult to demonstrate. This is partly due to the fact that even in the normal kidney it is not as definite and as well formed as the afferent vessel, for on its emergence it usually breaks up almost immediately into the capillaries of the intertubular network. It must be remembered too that in the great majority of the diseased glomeruli reduction or obliteration of the capillary bed in the tuft has caused a reduction in outflow and a consequent collapse of the efferent vessel. There is, therefore, an exaggeration of the normal disproportion in size of the two vessels of the glomeruli in the abnormal kidney. The difficulty in finding collapsed efferent vessels thus goes hand in hand with the relative ease with which dilated shunting Ludwig's vessels are found. In every case the efferent vessel if present is found to be of smaller diameter than the afferent (figs. 6, 26 and 28), and its delicate wall does not commonly show the extreme changes of sclerosis or degeneration that are seen in the latter.

The most striking change that affects the body of the glomerulus is variation in its size. All degrees of decrease in volume, apparently limited only by the smallest space that the fibrosed tuft may occupy when it is finally reduced to hyaline collagen, have been observed (figs. 4 and 5). It may be increased to sixty times its natural volume (fig. 31). In examination of the isolated intact glomerulus by the present method the cellular details of the abnormal process occurring in the substance of its tissues are invisible so that the cause of the enlargement remains obscure. Both inflammatory infiltration and hypertrophy of the tufts are possible factors, and although one cannot determine in a given isolated example which of these is present, it is evident from its shape and fatty content that changes other than a purely progressive hypertrophy are occurring. A supplementary study of histologic sections of the same kidney shows that practically all large glomeruli in terminal hemorrhagic Bright's disease are heavily infiltrated with inflammatory cells, and few, if any, show only the simpler hypertrophic change.

Alteration in shape of the glomerular body from the regularly round or oval contour of the normal structure is an equally striking abnormality. Egglike corpuscles with elongation through any diameter, pear-shaped bodies that may be fixed at either end to the afferent vessel, the production of flattened surfaces and of fissures and irregular lobulation result in almost every conceivable distortion (figs. 3 to 8, 13, 17, 20 and 21).

Though its cellular constituents are invisible, in many cases the abnormality of the tissues of the glomerular body may be recognized. The normal glomerulus is of an even gray opaque texture, and since the tuft fills the capsule almost completely very little internal structure can be made out. The great majority of glomeruli from the abnormal

kidney, however, contain a greater or less amount of fat which reflects the incident light with dazzling brilliancy. The appearance may be that of diffuse stippling with bright dots, in some instances so densely massed as to give the effect of a brilliant droplet of snow suspended, about to fall, on the twig of its rigid, fatty tinged crystalline afferent vessel (fig. 7). In others flecks or patches form an angular pattern which outlines the contour of the distorted tuft as it lies in its capsule; in still others the greater part of the body may be free with a single irregular broad patch of brilliancy (figs. 3, 5, 6, 8, 17, 27, 28 and 29).

As has been stated, the tuft itself is rarely seen in the normal glomerulus and then only with difficulty because it fills Bowman's capsule so completely. In the abnormal glomerulus, however, the capsule space is frequently distended and, as a result, the outline of the diseased tuft can easily be made out. All degrees of distention may be observed, from the production of a narrow irregular crescentic clear space, broadest at the tubular pole and decreasing toward the point of attachment of the tuft by its vessels, to conelike caps from the apex of which the tubule springs (fig. 6) or balloon-like appendages from which no tubule can be seen to arise (fig. 3).

The certain recognition of glomeruli whose tubules have been disconnected by the abnormal processes is difficult, for the attachment of the tube is normally weak, and in spite of considerable care fracture may occur during dissection. However, attention can be directed to such an atubular glomerulus before and during the dissection and the original absence of an attached tubule noted. When freed from the surrounding tissue the glomerulus may be turned with the needle and its entire surface inspected without the discovery of any interruption in the capsule. A careful examination is necessary in each instance before one can be certain that one is not dealing with an artefact. Even with this rigid examination many corpuscles were found that possessed no attached tubule. Further discussion of this observation will be given later.

THE PROXIMAL CONVOLUTION

Even in the normal kidney the general shape of the clustered mass of the proximal convolution is not constant. In the abnormal kidney, therefore, no characteristic change can be described for its general configuration. It is either smaller or larger depending on the nature of the change that has occurred in its constituent tubule. If there is a marked reduction in the diameter of the tubule there is usually a corresponding increase in the intertubular connective tissue, but such observations can be more clearly made in the reconstructed model [1] than in the teased specimen, for in the latter the tubule cluster is always more or less loosened from its original tightly packed condition. In

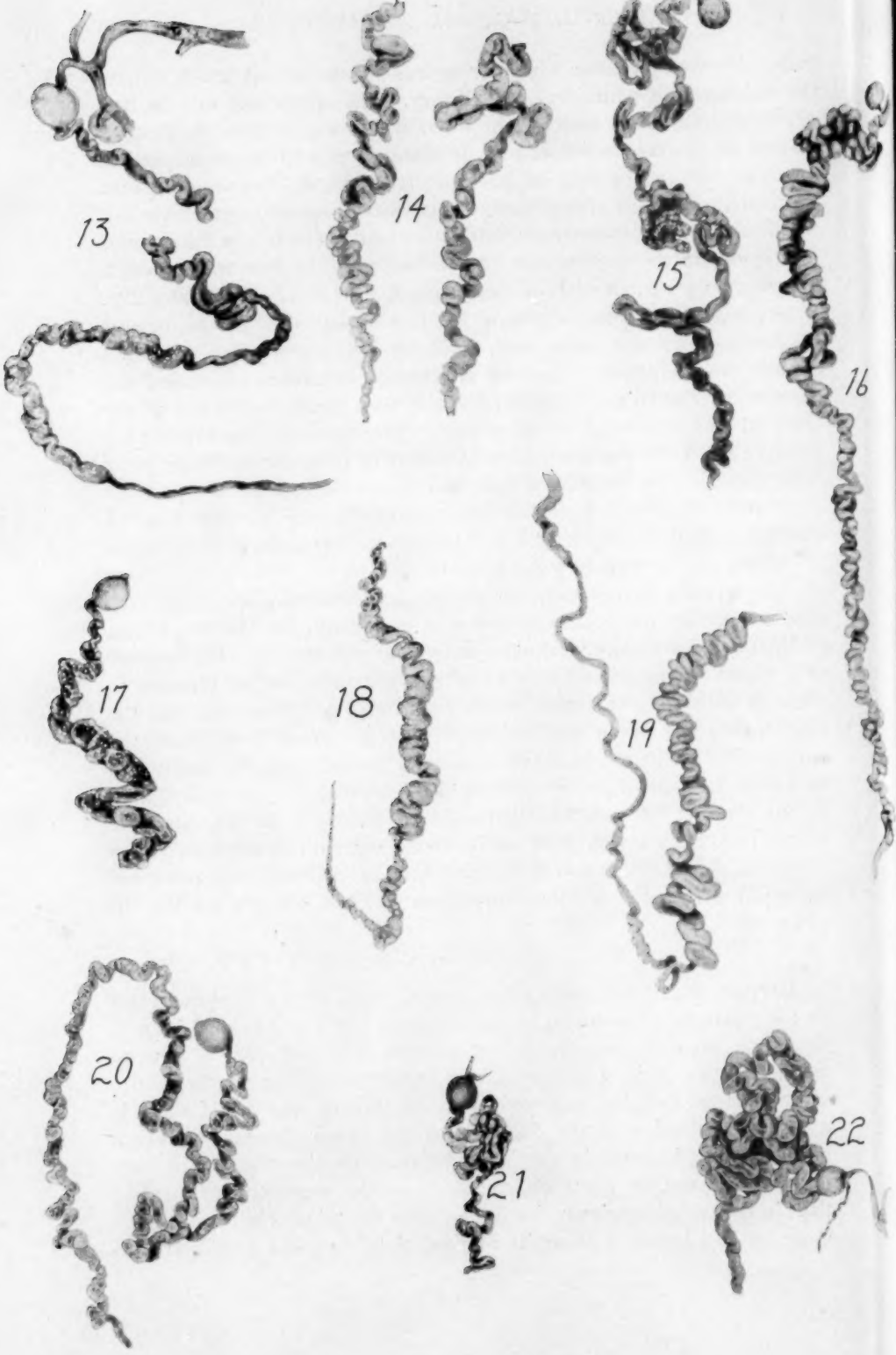
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Fig. 13.—The interlobular artery with afferent vessels to two glomeruli. From one arises the hypertrophied and hyperplastic proximal convolution. Its terminal segment shows a marked fatty change which does not, however, extend into the narrow limb of Henle's loop; × 15 (Addis and Oliver,[5] case 25, p. 294).

Fig. 14.—The terminal portions of two hypertrophied and hyperplastic convolutions in which there is also dilatation. The kinks of the tubules have been drawn apart to show the degree of hyperplasia; × 15 (Addis and Oliver,[5] case 32, p 325).

Fig. 15.—A complete hypertrophied and hyperplastic proximal convolution with fatty change in an isolated cluster of coils; × 15 (Addis and Oliver,[5] case 25, p. 294).

Fig. 16.—A complete proximal convolution showing marked hypertrophy and hyperplasia; × 15 (Addis and Oliver,[5] case 32, p. 325).

Fig. 17.—Glomerulus and portion of a proximal convolution, greatly dilated, showing a marked fatty change; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 18.—Terminal portion of a proximal convolution that shows an extreme hyperplastic kinking and dilatation. There is also a marked granular degeneration of its epithelial cells. The first portion of the narrow limb of Henle's loop is considerably dilated; × 15 (Addis and Oliver,[5] case 24, p. 288).

Fig. 19.—The terminal part of a hypertrophied and hyperplastic proximal convolution showing the complete narrow portion of Henle's loop and its passage into the broad ascending limb. The narrow segment of the loop is considerably dilated; × 15 (Addis and Oliver,[5] case 37, p. 348).

Fig. 20.—Glomerulus with a proximal convolution which shows almost pure dilatation; × 15 (Addis and Oliver,[5] case 25, p. 294).

Fig. 21.—Glomerulus with an atrophied proximal convolution. There is extreme irregular deformity of the tubule with marked fatty degeneration of its cells; × 15 (Addis and Oliver,[5] case 26, p. 298).

Fig. 22.—Glomerulus and vessels with a complete proximal convoluted tubule that shows a marked hypertrophy. A very long Ludwig's vessel is shown; × 15 (Addis and Oliver,[5] case 25, p. 294).

fact, the attempt was made in most cases to unravel the tubule purposely so as to show more clearly the details of its convolutions.

In the abnormal kidney the tubule presents little evidence of a "neck," the only exception being the production of a false neck in the examples in which the proximal convolution is greatly dilated with no corresponding thickening of its wall. The tubule contiguous to the glomerulus may remain undilated, thus forming a long narrow stretch that extends to the dilated portion (fig. 17).

The most striking changes noted in the proximal convolution are those of variation in size and fat content.

A reduction in diameter, the result of atrophy, may decrease the tubule to one half its normal caliber (figs. 21, 29 and 31). It is almost impossible to tease out these tenuous structures, especially since a fatty degeneration almost constantly accompanies the atrophy. Only fragments can be isolated completely. The best method therefore of studying these tubules consists in removing only partially the tissue which surrounds them. This is composed mainly of fibrous collagen which has softened and become translucent in the acid, and by the brilliancy of the excessive fat that is present in the atrophied epithelial cells the course of the shrunken tubule can be clearly observed and accurately followed. The loops are separated and widely spaced by the intervening scar tissue. This produces a simplification of the original complexity of the convolutions of the tubular mass and leads to such extremes as are seen in figures 29 and 31 in which the course of the tubules is almost straight.

The increase in the diameter of the proximal convolution may be due to actual hypertrophy with definite thickening of the wall of the tubule, to dilatation and a consequent thinning of the wall or to a combination of the two. If the enlargement is the result of hypertrophy, either alone or in combination with dilatation, there usually is an accompanying increase in the length of the tubule.

In the hypertrophied convolution an increase in diameter up to two and one-half times is frequently noted. The broad tubule preserves in a general way the normal arrangement of its convolutions (fig. 22). Throughout its length the tube appears either dense and solid, or with a narrow dark central streak which represents the lumen. Associated with this increase in the thickness of the epithelial cells there occurs in the majority of cases an increase in the length of the tubule. This is evidenced by the tortuosity of its convolutions, so that tightly formed secondary loops and kinks develop in the tubular mass which lies about the glomerulus. The cause of this lengthening of the tubule is the hyperplastic proliferation of its cells described in our previous study.

The complexity of the hyperplastic proximal convolution in the glomerular region is only an exaggeration of the normal condition, but

when the same process is noted in its terminal segment, which normally is a straight or at best a slightly undulating filament, a most striking appearance is produced. The thickened tube, at times twice its normal diameter, is folded back and forth on itself in tightly kinked, skeinlike bends, each so pressed on its neighbor as to have the appearance of a solidly fused irregular tube from which knoblike diverticula project (figs. 9, 11, 12 and 16). It is entirely impossible to follow the course of the tubule through these tortuous kinks, but they may be somewhat straightened out by stretching the tubule with the dissecting needles, and it is then seen that, although there are, in a certain sense, irregular projections from the walls, the tubule is in fact a continuous structure whose apparent diverticula are mostly due to its angular tortuosity. In figure 14 two enormous terminal portions of the proximal convolution are shown; these have been drawn out sufficiently to reduce their complex appearance. The passage into the narrow limb of Henle's loop may be seen at their lower ends.

The actual extent of the increase in the length of the proximal convolution by the development of these kinks is difficult to estimate. In typical examples of the normal tubule the terminal portion forms about one-third the length of the entire segment. In the abnormal kidney it is not unusual to find the hyperplastic tortuous terminal portion of equal length to the periglomerular mass. The significance of this disproportion will be considered later.

In the tubules just described there is little or no increase in the width of the lumen. In fact, the epithelial lining of the walls of many of them is so thick that the lumen cannot be seen at all. In others it is definitely dilated, at times measuring twice the normal diameter, but the wall is nevertheless thicker than normal. In these tubules hypertrophy and dilatation are evidently combined, and the result is the production of relatively enormous structures. Since hyperplastic lengthening is nearly always found accompanying the increase in thickness of the wall, such huge structures as that illustrated in figure 18 are not uncommon in certain kidneys. It will be noted that only the end fragment of a terminal portion of the proximal convolution is shown, and its passage into the narrow portion of Henle's loop is apparent. The periglomerular mass is, as a rule, relatively less massive, for it may be affected by the hypertrophy without marked dilatation.

Other proximal convolutions show pure dilatation of their lumens. The wall is therefore stretched to a membrane of almost endothelial-like thinness, which, when the tubule is isolated, falls in folds on itself as it collapses. It is extremely difficult to tease out these delicate structures in any great length, but figure 17 shows a part of an extreme example while figures 20, 26 and 28 present tubules showing varying degrees of dilatation without any thickening of their walls. Figures 23

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Fig. 23.—Complete short loop nephron. The glomerulus is greatly enlarged and the proximal convolution dilated with little evidence of hyperplastic kinking. The narrow limb of Henle's loop is dilated and passes into the broad ascending limb which ends in a dilated and empty distal convolution; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 24.—A loop of Henle arising from a hypertrophied and hyperplastic proximal convolution; × 15 (Addis and Oliver,[5] case 24, p. 288).

Fig. 25.—A loop of Henle from the long loop type of nephron, including the terminal portion of the proximal convolution. The narrow portion is moderately dilated. The ascending broad portion is irregularly dilated and contains some solid material; × 15 (Addis and Oliver,[5] case 24, p. 288).

Fig. 26.—Greatly enlarged glomerulus with fatty change. The afferent and efferent vessels are well shown. The proximal convolution shows a simple dilatation. There is a marked fatty deposition in an isolated group of coils; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 27.—A glomerulus with complete proximal convolution showing a combination of atrophy, dilatation, hypertrophy and hyperplasia; × 15 (Addis and Oliver,[5] case 6, p. 197).

Fig. 28.—The glomerulus is enlarged. The efferent and afferent vessels are well shown along with Ludwig's vessel. The tubule is dilated and shows considerable fatty change; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 29.—Two glomeruli with portions of markedly atrophied proximal convolutions. Note the simplification of the convolution pattern; × 15 (Addis and Oliver,[5] case 23, p. 283).

Fig. 30.—Complete short loop nephron showing dilatation of the proximal convolution. The dilatation extends into the narrow limb of Henle's loop and its ascending portion and the convolution. The latter is empty; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 31.—Tremendously enlarged glomerulus, 60 times the average normal volume. There is a moderate atrophy of the proximal convolution with simplification of the normal looping of the convolutions; × 15 (Addis and Oliver,[5] case 38, p. 354).

Fig. 32.—The greater part of a proximal convolution showing hypertrophy, hyperplasia and dilatation combined. There is a marked fatty change in the terminal portion which ends abruptly as the tubule becomes the narrow segment of Henle's loop; × 15 (Addis and Oliver,[5] case 14, p. 288).

and 30 are of interest since complete short loop nephrons from the glomerulus to the collecting tubule are intact. It is significant that such dilated broad tubules seldom show the hyperplastic kinking so common with the hypertrophic increase in diameter, but are characterized by a definite decrease in the complexity of their convolutions. In figure 20, though the original course of the tubule has been disentangled, it is readily apparent that no condition approaching the tortuosity shown in figures 9, 11, 12 and 16 could ever have existed.

Associated with dilatation, particularly in tubules which show this passive increase in diameter with no evidence of progressive hypertrophic change, fatty accumulations are seen in the thin epithelial walls (figs. 17, 20, 23, 26 and 30). The droplets of fat are usually diffusely sprinkled and may extend throughout the entire length of the isolated segment. In other instances the fat is sharply limited to a few contiguous coils (fig. 26), so that a loop passes out of the area of change, becomes free and then, reentering it, becomes again involved. Thus irregular small stretches of fatty deposit in the tubule, interrupted by normal segments of epithelium, are produced.

It is much less common to find fatty accumulations in the proximal convolutions that show increase in size from an actual hypertrophy of their walls. However, examples may be found, either with a restricted cluster of loops filled with refractile droplets (fig. 15) or with irregular small patches scattered along the greater part of the course of the tubule. Not infrequently it is the end part of the terminal segment of the convolution that is involved, the fatty metamorphosis beginning abruptly and extending downward to end with equal suddenness where the proximal convolution passes into the narrow limb of Henle's loop (figs. 13 and 32).

The change in the proximal convolution, whether taking the form of an atrophy, a hypertrophy, a dilatation or a hyperplasia, has been described so far as affecting this segment in a single manner, the result being the production of a tubule that is either greater or smaller than the original structure. This often occurs, but in many instances single units show a combination of all these changes. In figure 27 a proximal convolution is atrophic in its first part; it then assumes a normal caliber, which is increased by a definite hypertrophy, while its terminal portion is markedly kinked by hyperplastic growth. Similarly in figure 17 the first portion of the convolution is reduced in thickness but suddenly increases in diameter with a tremendous dilatation. All conceivable combinations of these changes have been observed and, along with the isolated occurrence of fatty change in limited and contiguous loops of the tubule, give evidence of the importance of local processes the significance of which will be considered later.

THE LOOP OF HENLE

The division of the nephron into two types, those with long loops of Henle and those with short, can be easily made in the abnormal kidney. Although, as their names indicate, the length of the two types is a distinguishing feature, this characteristic is only relative, and the criterion for their identification in the human kidney is the location where the bend of the loop and consequent reversal of direction occurs. In the case of the long loop the bend is situated in the inner zone of the medulla. Since only the narrow segment of the loop reaches this depth, the bend is invariably in that part of the tubule. Short loops reverse their direction in the outer zone and even at times in the cortex. In these regions of the kidney the broad segment is present, and the actual bend always occurs in it. Examples of short-looped nephrons have been demonstrated completely; that is, the nephron from the glomerulus through the first part of the collecting system has been isolated intact by dissection (figs. 10, 23 and 30). It is important to note that in the human kidney the short loops are much more frequent than the long; according to the counts of Peter they are seven times more common. As has been the experience of those who worked with the normal human kidney, we have been unable to isolate a long loop completely, since the tenuous narrow portion is a structure of great length and fragility. All the various parts of these loops are, however, easily obtained.

THE NARROW SEGMENT OF THE LOOP

The narrow segment which in the long type of nephron forms a portion of both the descending and the ascending limb retains its normal characteristics to a remarkable degree in the abnormal kidney. In short loops it may exist as a short clear segment of its usual diameter separating the hyperplastic proximal convolution from the broad limb of the loop (fig. 10), or in others it may, as happens in normal kidneys, be entirely missing.

A curious effect on the direction of the narrow segment is produced by hyperplastic processes in the terminal portion of the proximal convolution. Not all of the increase in length of the tubule is taken up by the kinking that occurs in it, and as a result there is a definite extension toward the medulla of the kidney. Peter has emphasized the fact that the actual bend of the loop in the short variety of the human nephron is always in the broad segment, and the normal direction of the narrow segment is, therefore, always descending. But in some hyperplastic short loop units there results an inversion of this direction of the narrow segment, for the advancing terminal portion of the proximal convolution grows down past the original bend of the loop, drawing the narrow segment after it. It is only by such a process that the appearance shown in figure 19 can be explained. In the latter the

whole length of the narrow segment is shown to its termination in the broad segment. The bend of the loop is situated in it, close to the end of the hyperplastic terminal portion of the proximal convolution, and its entire course is ascending, so that it forms the greater part of the distal limb of Henle's loop.

Narrow segments that lie closely pressed among the hyperplastic kinked terminal portions of the proximal convoluted tubule are often molded into a similar wavy course (figs. 19 and 24). Part of this kinking may be due to hyperplastic growth in the narrow segment itself, but the appearance noted during the dissection indicates that the greater part of the change is a passive one.

Peter describes the occurrence of crystals in the narrow segments of the loop. We have noted them—in some cases they are a definite brick red—but we have not noticed any significant increase in their amount.

THE BROAD SEGMENT OF THE LOOP

The actual transition from the narrow to the broad segment in the normal kidney is determined more by the character of the epithelial wall than by the caliber of the tube. The clear cells of the narrow portion are replaced by the darker opaque ones of the broad segment. But in the abnormal kidney in which degenerative changes are apt to occur throughout the epithelial lining of the tube the exact point at which a narrow segment becomes broad may be indistinct. In figure 10, depicting a complete short loop nephron with hypertrophy of the proximal convolution, the relatively clear appearance of the narrow segment is preserved so that the division is quite apparent. In figure 23 another complete nephron is illustrated. From the end of the dilated fatty proximal convolution arises the narrow segment which passes downward to bend abruptly back forming the loop. From there the ascending distal limb, comprising the narrow and broad segment, follows, but it is difficult to determine the exact point of transition between the two. The broad limb finally ends in the distal convolution. It is somewhat tortuous, but the contours of its walls are even. In figure 25 a narrow segment from a long loop containing the bend is shown. It grows increasingly thicker as it ascends to change without any exact line of demarcation into the broad segment. The latter is only slightly increased in caliber, and save for the moderate tortuosities is essentially normal.

Tortuosities or varices and dilatation are the most frequent abnormalities in the broad segment. We have never found any appearance that could be interpreted as evidence of hypertrophy or hyperplasia. In figures 24, 25, 39 and 42 varying degrees of varix formation are present in segments otherwise only moderately dilated. The different appearance of these irregularities from the even hyperplastic kinking observed

in the proximal convolution is obvious. Not infrequently the irregular dilatations contain coagulated material, which increases in amount until the distal convolution is reached. This portion of the nephron, as we shall see later, is commonly filled completely with solid substance.

A more even and general dilatation of the broad segment with a consequent thinning of its wall is also frequently observed. In figure 30 a short loop nephron shows the proximal convolution ending in an extremely short narrow segment. The bend of the loop occurs in the broad segment. This portion, greatly and fairly uniformly dilated, is apparently empty [7] and ascends in broad waves to pass into the distal convolution.

Whether or not dilatation occurs behind an obstruction of the tubule appears to depend on more factors than are included in the obstruction to flow alone and will be discussed later. It will be sufficient at present to note its varying occurrence in the more distal portion of the tubule in which plugging of the lumen becomes progressively frequent. In figures 33, 38, and 43 varying degrees of dilatation of the ascending limb are present, and in most examples the distal convolution contains solid material. In the broad segments that show the greatest degree of dilatation, however, the widened lumen is not empty but is filled with a translucent coagulum so transparent that at first glance the tubule appears empty. In other instances the clear substance is flecked with minute striations of more opaque material that gives a feathery appearance to the whole mass. At times (fig. 44) the distention is tremendous, the diameter of the segment being four times the normal. The wall is greatly thinned, and the smooth contours of the tube swell and project in a manner entirely different from the irregular varices previously described.

To sum up the abnormalities found in the loop of Henle, including both its narrow and broad segments, it may be stated that only passive changes have been noted, especially distortion and dilatation. No hyperplastic or hypertrophic changes were observed, the only exception to this statement being the secondary, and therefore in a sense passive, lengthening of the narrow segment when it is drawn downward by the actively growing hyperplastic terminal portion of the proximal convolution. There is a great contrast, therefore, between the pathologic processes concerned in these two different divisions of the nephron.

THE DISTAL CONVOLUTION

The term "distal convolution" is in one sense unfortunate for it gives the impression that this portion of the nephron is the morphologic

7. The term "empty" is applied to the appearance of lumens that were formerly filled with clear fluid or urine that has left no trace in the fixed material.

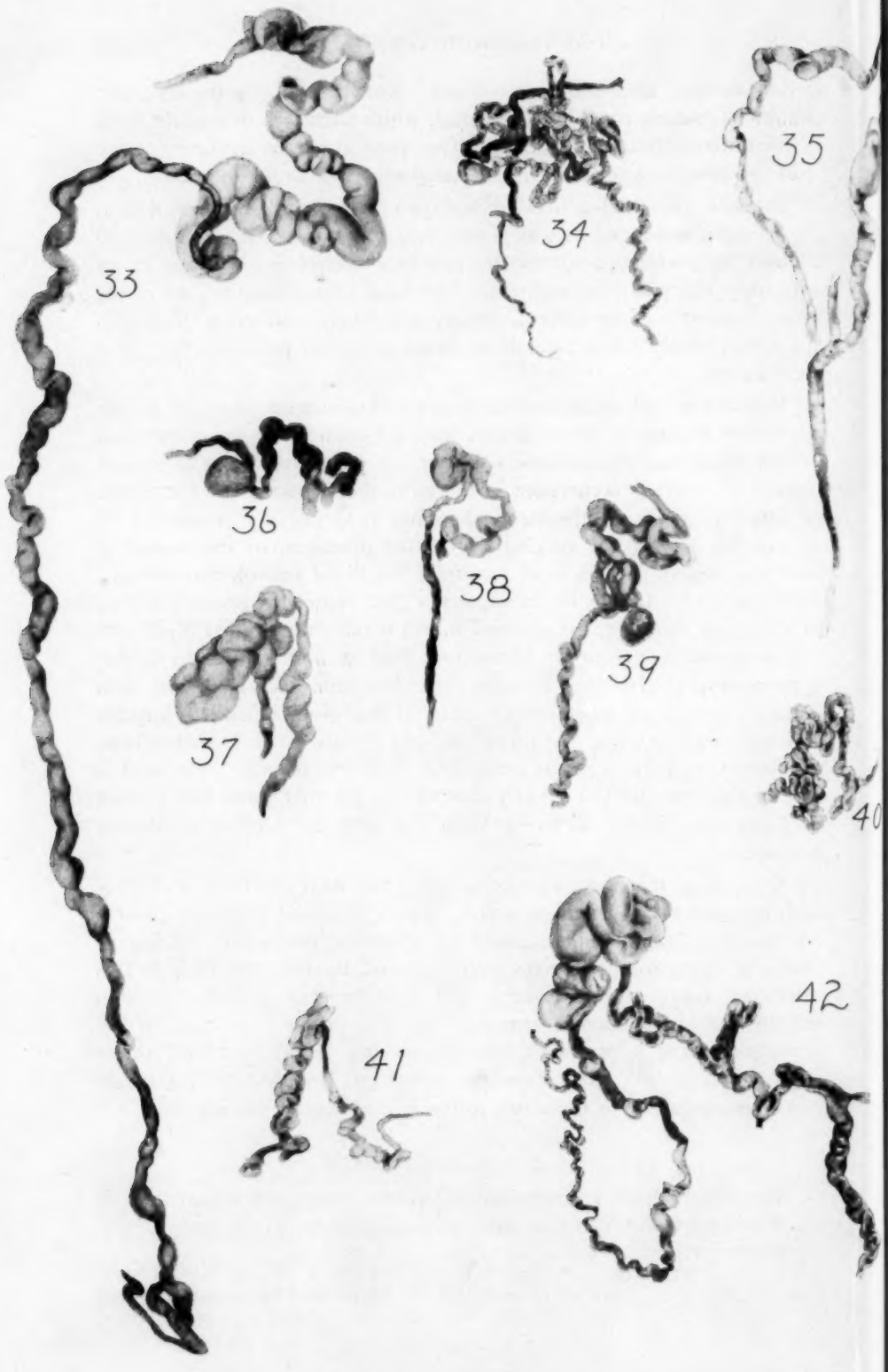
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Fig. 33.—Tremendously enlarged distal convolution packed with heterogeneous débris. The ascending limb of Henle's loop is greatly dilated and empty. The dilatation extends around the bend into the narrow limb of the loop; × 15 (Addis and Oliver,[5] case 25, p. 294).

Fig. 34.—The glomerulus and the periglomerular mass of the proximal convolution. There is a considerable fatty degeneration in this portion of the tubule. At the left the broad limb of Henle's loop ascends to the region of the glomerulus where a dilated empty distal convolution finally passes to the right by its connecting tubule; × 15 (Addis and Oliver,[5] case 42, p. 370).

Fig. 35.—At the left a dilated ascending limb of Henle's loop passes into the distal convolution, followed by the connecting piece and collecting tubule. All these tubules are packed full of highly refractile granular débris. The lower part of the collecting tubule is, however, constricted and empty; × 15 (Addis and Oliver,[5] case 37, p. 348).

Fig. 36.—Greatly enlarged glomerulus to which is adherent a distal convolution that is in part empty but a few loops of which contain granular débris; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 37.—On the right the ascending limb, tremendously dilated with refractile material, passes into a dilated distal convolution stuffed with the same type of débris. The connecting piece runs directly down from the cluster of its coils; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 38.—The distal convolution above is packed with débris. The ascending limb in Henle's loop is dilated and empty, as is the connecting piece; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 39.—Another distal convolution irregularly filled with material. Note the adherent glomerulus; × 15 (Addis and Oliver,[5] case, 27, p. 302).

Fig. 40.—On the left the entrance to a distorted plugged distal convolution that ends in the connecting piece on the right; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 41.—A typical deformity in the plugged distal convolution. On the right is the empty connecting piece; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 42.—A short nephron complete except for the glomerulus and portion of the proximal convolution. The latter shows a marked atrophy and fatty degeneration. The ascending limb of Henle's loop passes into a greatly distended distal convolution which is packed and distended with débris. The connecting piece and place of origin of the collecting tubule are empty; × 15 (Addis and Oliver,[5] case 27, p. 302).

equivalent of the proximal convolution. As Peter showed, this is far from being the case, since the distal convolution consists at best of a few poorly formed loops, never approaching in complexity the complicated system of the proximal convolution (fig. 2). The term is, however, firmly established in English nomenclature, and we shall therefore use it, although it will be apparent in the presentation that follows that just as in the normal kidney the two convolutions, proximal and distal, are morphologically different, so in the abnormal organ they differ strikingly both as to the nature of the processes which affect them and in the final structural result produced.

The broad limb of Henle's loop passes into the first irregularities of the distal convolution at the level of the glomerulus from which the nephron arose. As Peter has shown, the tubule is attached quite firmly at this point to the capsule of the corpuscle and is frequently found still adherent to it when isolated by dissection. The same is true in the abnormal kidney (figs. 9, 36 and 39).

The most common abnormality in the distal convolution is simple dilatation. Gradually increasing distention distorts the lumen until its diameter may be over five times that of the normal (figs. 9, 23, 30, 34 and 45). The wall, greatly stretched, shows no sign of a compensatory thickening but is almost transparent. Figure 34 shows such a dilated distal convolution *in situ* with its relations to the glomerulus and the proximal convolution. The latter is filled with fat, and thus contrasts strongly with the translucent thin-walled distal segment with which it is entangled.

In the normal kidneys studied, which are all from young adults, we have found very few of the varicose distal convolutions described by Peter, while in the abnormal kidneys irregularity is consistent and exaggerated far beyond anything that he observed. It is interesting to note in passing, therefore, that he found such structures with increasing frequency in the kidneys of older persons. In the abnormal tubule the irregularities take the form of fusiform swellings that taper to narrow necks, bulbous varices that jut out in grape cluster fashion from the tubule, or spherical appendages (figs. 9, 23, 30 and 41).

The other abnormality noted in the distal convolution is found intimately associated with dilatation. It consists of a filling of the distended and distorted loops with solid débris so that the flexible tubule which normally bends and sways with the motion of the slightest current in the suspending water is transformed into a solid inflexible tortuous structure. The least attempt to rearrange its convolutions with the dissecting needles results in the fracture of its brittle substance. The solid material consists of a varying mixture of fatty substances that are highly refractile and irregular granular masses which have the

appearance of coagulated albuminous material. All degrees of occlusion occur, from a stuffing of a single loop or a diverticular appendage of the main tube to solid packing of complete convolutions (figs. 37, 38, 39, 42, 43 and 46). Examples are also found in which alternation of empty and plugged loops occurs (fig. 40). The filling of the lumen may extend beyond the limits of the distal convolution downward into the broad ascending limb of Henle's loop, an appearance that has been previously described (figs. 35 and 39).

A characteristic of the solid material that fills the lumen of this portion of the nephron is its lack of homogeneity. Its density varies irregularly, more solid opaque masses alternating with lighter substances. Adjacent loops, for example, often show this appearance strikingly (figs. 39, 40 and 43). Another peculiarity is the sudden and abrupt ending of these deposits. A sharp end of solid substance, either straight or rounded, projects into the dilated portion that is free from débris. This is particularly well illustrated in figure 33, which shows a veritably gargantuan distal convolution packed full of heterogeneous material. At both limits of the accumulation the sudden cut-off ends abut into the empty portion of the tubule. The usual variation in the density of the occluding substance is also evidenced in this example.

The common accompaniment of the collection of débris in the distal convolution, namely, the dilatation of the fluid-containing, broad limb of Henle's loop, is apparent in figure 33. It is stretched by internal distention to at least four times its normal diameter, and even the narrow segment of the loop proximal to the bend is definitely distended.

Solid material of an entirely different character from this heterogeneous mixture of fat and granular substance is also found in the dilated distal convolutions. This consists of the almost perfectly translucent jelly-like material that has been described as at times filling the distended broad limb of Henle's loop. It may, in fact, fill a considerable length of tubule, including the dilated broad limb of Henle's loop, the distal convolution, the connecting tubule and a large portion of the collecting tubule (fig. 44), yet throughout show no variation in its clear translucency. Moreover, there is never any interruption of it from loop to loop as was not infrequent in the distal convolutions that were filled with the heterogeneous débris-like material. As will be emphasized later, it appears as if the contents of a tubule dilated and filled with a coagulable fluid had congealed at a given definite time throughout its entire extent.

Peter describes the occurrence of large numbers of crystals in the distal convolution. We have seen them, but have found no excessive collection of them. It may be that in our abnormal material they are obscured by inclusion within the dense opaque débris.

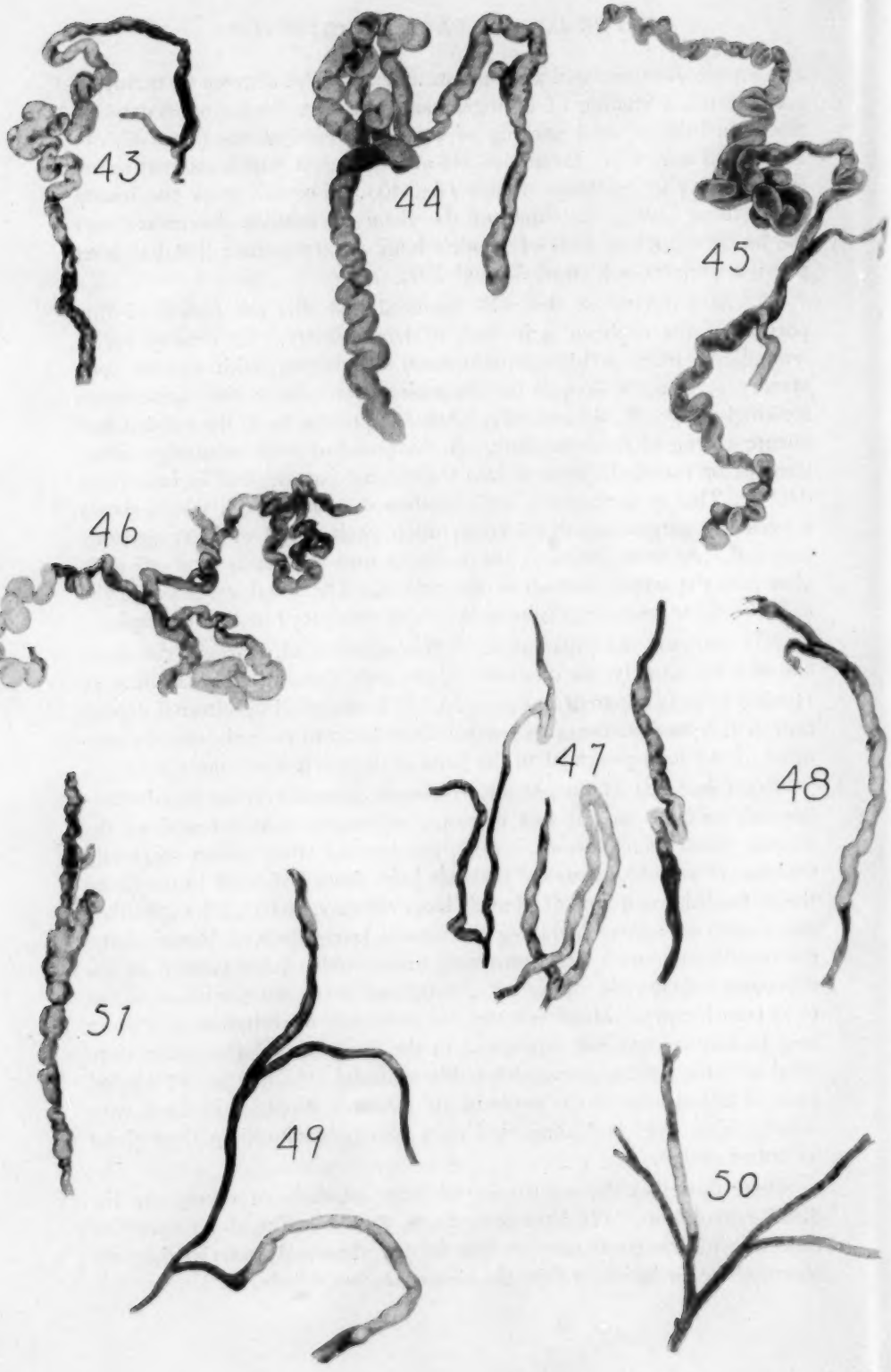
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Fig. 43.—A plugged distal convolution with marked dilatation and only partial filling of the ascending limb below. Above, a dilated connecting piece and collecting tubule; × 15 (Addis and Oliver,[5] case 25, p. 294).

Fig. 44.—Tremendously dilated ascending limb, distal convolution, connecting piece and collecting tubule. The entire tubule is distended with clear coagulated jelly-like material; × 15 (Addis and Oliver,[5] case 35, p. 339).

Fig. 45.—Two distal convolutions and their connecting tubules joining to form the collecting tubule. Both are greatly dilated but empty; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 46.—Three distal convolutions, two plugged and one empty, and their junction to form a collecting tubule; × 15 (Addis and Oliver,[5] case 27, p. 302).

Fig. 47.—Traplike loops in the peripheral collecting tubules. The loops are filled with refractile débris; × 15 (Addis and Oliver,[5] case 37, p. 348).

Fig. 48.—A peripheral collecting tubule containing a castlike mass of solidified débris. Note the constriction below the occluding material; × 15 (Addis and Oliver,[5] case 32, p. 325).

Fig. 49.—Irregularly dilated and constricted peripheral collecting tubule. One branch is filled with castlike substance; × 15 (Addis and Oliver,[5] case 37, p. 348).

Fig. 50.—Undeformed peripheral collecting tubules containing a hyaline cast. Contrast the ease with which such a cast might escape with the conditions of the previous three specimens; × 15 (Addis and Oliver,[5] case 42, p. 370).

Fig. 51.—Sacculated deformity of peripheral collecting tubule; × 15 (Addis and Oliver,[5] case 32, p. 325).

THE CONNECTING TUBULE

Peter describes the *Schaltstück,* or distal convolution, as consisting of two divisions, the first and the second. The latter, differing very little from the first in its structure, passes into the origin of the collecting tubule. This second division may be called the connecting piece, for there is a certain advantage in preserving its individuality in describing the nephron of the abnormal kidney. In most cases it consists only of the less twisted portion of the tubule that joins the definite loops of the distal convolution to the collecting tubule, which also does not differ greatly from it. The separation into these several parts is made chiefly by the general configuration and the direction of a continuous tubule. This is particularly true in the abnormal kidney when all these portions are dilated or when they are filled with what appears as a clear coagulum (fig. 44).

In many instances, however, the connecting piece is not dilated, and therefore stands out in marked contrast to the greatly dilated distal convolution that precedes it. Especially is this contrast striking when the loops of the convolution are filled with mixed débris and this material ends abruptly to leave the constricted connecting piece empty (figs. 33, 38, 40, 42 and 43). In such cases the large distorted and plugged coils of the distal convolution end at both extremities in narrow, empty tubes, proximally in the broad limb of Henle's loop and distally in the connecting piece.

THE COLLECTING SYSTEM

The origin of the collecting system is readily observed in the abnormal kidney, perhaps even more easily than in the normal organ, for the dilated distal convolutions stand out prominently when filled with solid material, and their passage by means of the connecting tubule into the peripheral collecting tubule is plainly evident. In figure 45 an enormously dilated but empty distal convolution joins by means of its connecting piece with another connecting piece the convolution of which is broken away and so forms the collecting tubule. In figure 46 the connecting piece of two distal convolutions join to form the duct to which a third convolution is soon added.

The collecting tubules just described have appeared as empty tubes. Not infrequently those distal convolutions that are greatly distended with translucent jelly-like coagulum pass into a collecting tubule which is equally dilated and filled with a continuous mass of the same material (figs. 44 and 54). The tubule shown in the lower portion of figure 54 contains mixed débris.

The collecting tubule may also contain, from its origin, the heterogeneous fatty and granular substance that so frequently fills the distal convolutions. In figure 35 the ascending limb of Henle's loop, the distal convolution, the connecting tubule and a great length of the col-

lecting tubule are shown to be densely packed with débris. The whole structure when isolated was rigid and easily fractured. A connecting tubule from another nephron containing the same material joins the duct. Accumulated matter has irregularly distended its lumen, and this distention ends suddenly while the tubule continues diminished in caliber and empty. Such dilatations filled with solid material lying proximal to an empty lumen of lesser diameter are frequently found in the collecting system.

As in the normal kidney, the peripheral collecting tubules continue independently down through the depths of the cortex and in the outer zone of the medulla join to form the central tubules. From there on a repeated union of ducts by the typical tuning fork junction described by Peter lessens their number with an increase in the size of the lumen of the resulting tubule.

In its course through the cortex the peripheral collecting tubule may be joined by the connecting piece of an occasional distal convolution. Even in the normal kidney its course is, however, not always direct, for knotlike kinks occur as well as retrograde loops which turn back toward the cortex for a short distance and then return to their medullary direction. In the abnormal kidney these kinks and loops assume a considerable importance because they are often filled with solid granular material similar in appearance to that observed in the distal convolutions (fig. 47). The tubule in the loop is distorted and thrown into irregular bulging segments as if it had been actually stuffed by accumulating débris under a considerable pressure. One gains the impression that the loop has acted as a trap for material carried to it by the stream of the urine, for the lumen below the obstruction is smaller than that occupied by the occluding plug.

The normal central collecting ducts which first arise at the junction of the outer and inner zone of the medulla are evenly contoured tubes the lumens of which become larger with each fusion. Fairly normally preserved ducts of this character may be found in the abnormal kidney, and within them may be seen solid material firmly molded into clear hyaline casts of the lumen (fig. 50). But the majority of the central ducts of the abnormal kidney lack their normal characteristics, for they are irregular both in contour and in caliber. The irregularity of their contour consists of increases or decreases in diameter that alternate in no definite order. The lumen of such ducts may or may not contain débris (figs. 48 and 49).

A more striking appearance is offered by the ducts in which the dilatation and constriction affect the contour of the tube in a more regular and patterned fashion. Such distortions may take the form of sacculated bulgings, at times almost spherical, while in other instances they are blocklike, or all manner of irregular transitions from one type

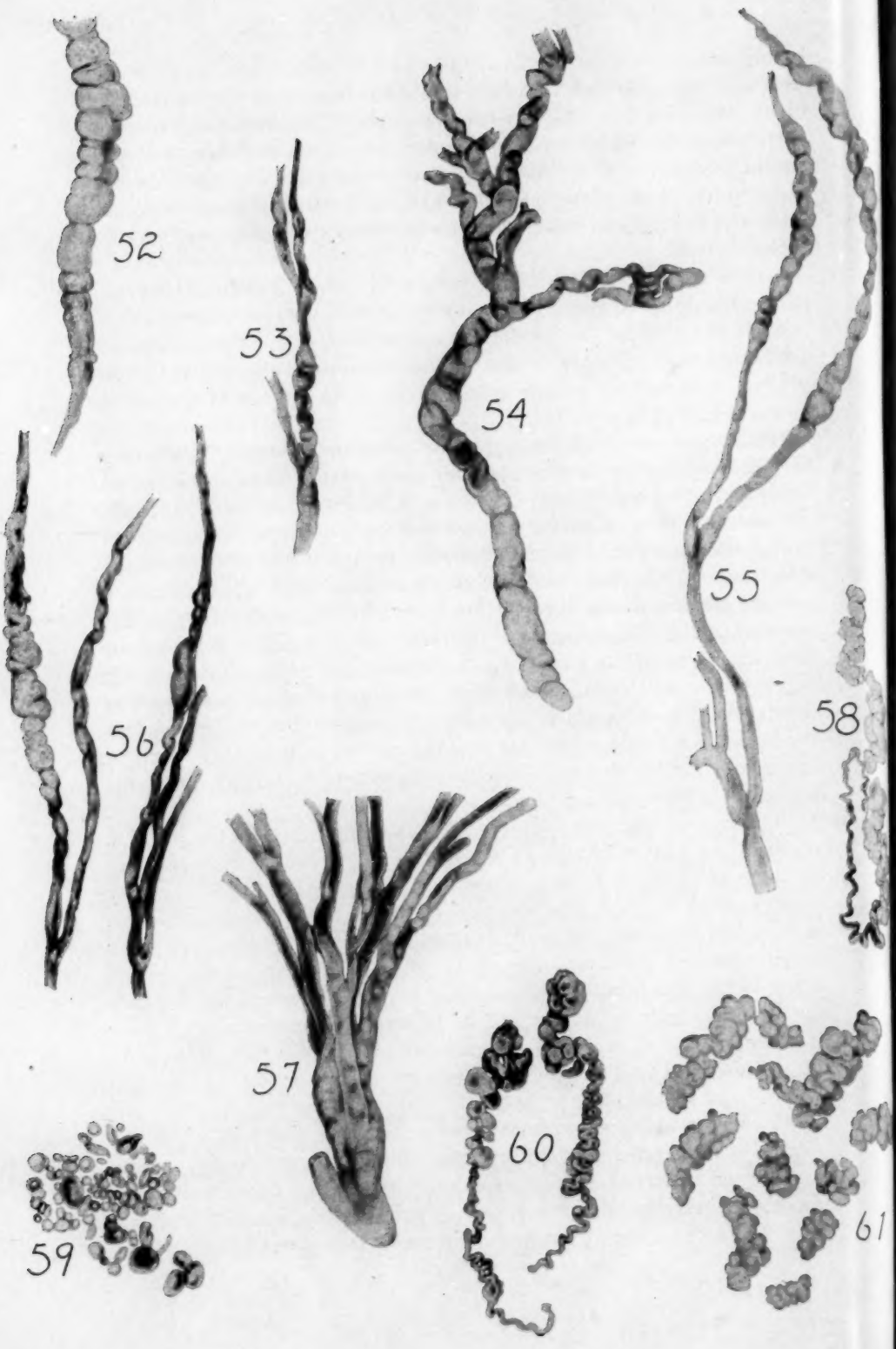
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Fig. 52.—Large central collecting tubule showing the typical fusiform sacculated deformity. The segments are filled with débris. Note the narrow constricted portion below; × 15 (Addis and Oliver,[5] case 32, p. 325).

Fig. 53.—Central collecting tubule showing fusiform and spherical deformity with irregular constrictions of the lumen; × 15 (Addis and Oliver,[5] case 32, p. 325).

Fig. 54.—The origin of a collecting tubule. The upper portion is dilated and filled with homogeneous, clear, jelly-like material. In the lower portion an obliteration by refractile débris fills the lumen; × 15 (Addis and Oliver,[5] case 37, p. 302).

Fig. 55.—Irregularly deformed central collecting tubules filled with débris that contains crystals and a spherolith; × 15 (Addis and Oliver,[5] case 32, p. 325).

Fig. 56.—Collecting tubules showing the fusiform type of deformity. One tubule is filled partially with débris and crystals; the others are empty; × 15 (Addis and Oliver,[5] case 32, p. 325).

Fig. 57.—The termination of the collecting system in a duct of Bellini. Note the casts filling the terminal collecting tubules. The footlike process is composed of the epithelium which lines the operculum; × 15 (Addis and Oliver,[5] case 6, p. 197).

Fig. 58.—Terminal portion of a dilated hypertrophied and hyperplastic proximal convolution that has been separated by the pathologic processes into three segments. The lower one continues on into the narrow portion of Henle's loop; × 15 (Addis and Oliver,[5] case 6, p. 197).

Fig. 59.—Cystlike structures resulting from multiple disruption of tubules. They are filled with coagulated material; × 15 (Addis and Oliver,[5] case 36, p. 343).

Fig. 60.—Terminal portions of the proximal convolution showing extreme deformity with sacculation; × 15 (Addis and Oliver,[5] case 6, p. 197).

Fig. 61.—Isolated vesicles resulting from the disruption of hypertrophied and hyperplastic terminal portion of the proximal convolution; × 15 (Addis and Oliver,[5] case 6, p. 197).

to the other are observed in the course of a single tubule (figs. 51, 52, 53, 55 and 56). Such distorted ducts may be empty. In many examples the sacculation is so extreme that the duct is transformed into a segmented flattened structure three times as wide as it is thick. The segments are connected to each other by narrow communications and are arranged so that their size uniformly increases to a maximum perhaps four or five times that of the original duct and then decreases until the normal diameter of the tubule is again reached. In this manner a long fusiform sacculated dilatation of the tubule is formed which is nearly always filled to a greater or less extent with granular débris. In the débris crystals may be found in great number, some colorless minute needles, others a bright red. Spheroliths also are not uncommon (figs. 55 and 56).

The number of the central collecting ducts is eventually reduced by fusion, and they join to form the terminal duct of Bellini. Peter was unable to isolate this structure in the human kidney because of the fragility of its thin wall that encloses so great a cavity. In the abnormal kidney it is usually packed with heterogeneous débris so that its contents support its walls, and this facilitates dissection. In figure 57 the larger collecting ducts rapidly join by pairs until three large trunks are formed. These three trunks unite to form the duct of Bellini, a bulbous structure which constricts and then opens into the pore of the area cribrosa. A portion of the epithelial lining of the pore has remained attached to the margin of the opening of the duct.

The terminal collecting tubules contain solid material in masses which from their definitely molded cylindric form may be designated as "casts." The contours of these large tubules are not distorted, and it seems quite possible therefore that such casts might be swept with the urine into the bladder. The capacious cavity of the duct of Bellini is also filled, though its content is not consolidated into a definite plug or "cast" of the lumen, but consists of loosely packed clumps of granular débris. Thus are formed the huge but fragile "renal failure casts" the appearance of which in situ has been previously illustrated in histologic section.[8]

And so, reaching the pelvis of the kidney, ends the course of the abnormal nephrons and their terminal ducts.

STRUCTURES PECULIAR TO THE ABNORMAL KIDNEY

The structures so far described, though in many instances greatly distorted from their original morphologic condition, retain the fundamental characteristics of the normal nephron. Other structures found in the abnormal kidney, though derived from normal architectural units

8. Addis and Oliver,[5] fig. 17, p. 139.

by the action of the pathologic processes, nevertheless are peculiar to it, for they have no counterpart in the normal organ. The production of these abnormalities is due mainly to the action of the chronic and progressive inflammatory process which, occurring in the interstitial frame-work of the organ, exerts a continuously increasing pressure as the products of the reaction increase. To this deleterious factor is added the disrupting and distorting force that develops when the inflammatory tissue begins to contract. The distortions of the nephron heretofore described were due in part to such forces; the most severe result of them is an actual disruption of the unit.

We have already described how the glomerulus may be pinched from its tubule and lie free as an isolated object still attached to its vessels. If the tubule may be interrupted at its exit from the glomerular body, a point of structural weakness, such an interruption is also possible at any place or at repeated places in its course.

In our earlier histologic study by means of sections of these same kidneys we found certain cases in which large areas of the renal parenchyma were composed of closely grouped cross-sections of tubules. These areas occurred most frequently in the outer zone of the medulla but were also present in the cortex. The tubules that filled them were lined by an intact epithelium of an atrophic and atypical appearance, and their relatively large lumens contained coagulated material that was hyaline, though central condensation and lamination of its substance could at times be seen. Figure 62 shows the appearance in section of these tubules, and another example may be seen in the previously published monograph.[9]

There is something about the arrangement in the section of these tubules that arouses the curiosity if not the suspicion of the observer as to their actual nature. When examined by microdissection the reason for their peculiarity is apparent (fig. 59). The "areas filled with tubules" are not groups of closely packed tubes but large masses or irregular collections of small round or oval cysts, the diameters of which vary within the limits observed in the tubular structures of the abnormal kidney. They lie in closely clustered masses of considerable size that may contain no other elements of the original renal structure. When macerated material is examined in which the action of the acid has only softened and made translucent the collagenous material of the scar tissue that always surrounds them they appear not unlike the jellied egg clusters of certain Amphibia. Each cyst contains solid clear material which, as in the stained histologic section, may show central condensations.

Any doubt that these cysts arose from the disruption of tubules is removed by a careful examination of their shape. Although the major-

9. Addis and Oliver,[5] fig. 38 A, p. 356.

ity are perfect spheres or oval bodies, examples that are definitely elongated fragments of tubes are found occasionally. Others of considerable length are irregularly fusiform or pear-shaped.

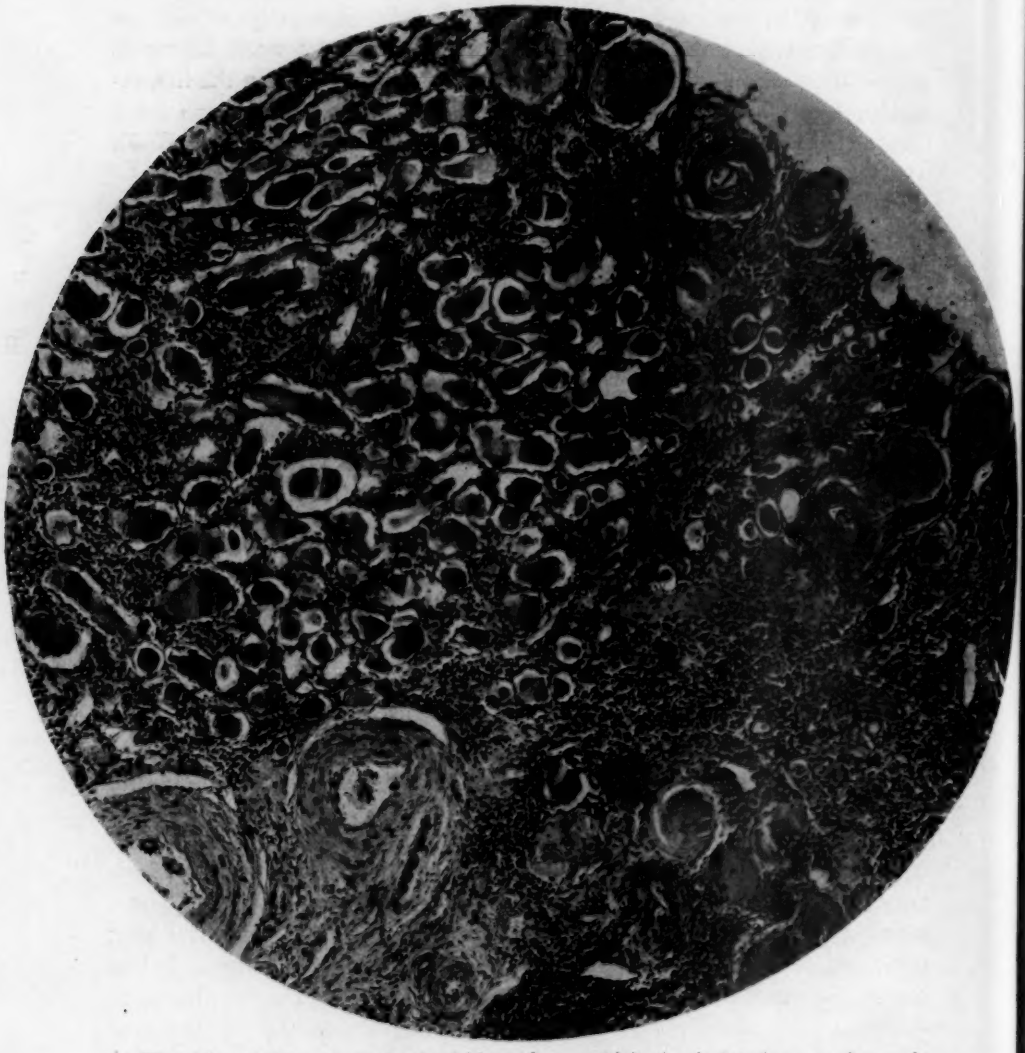

Fig. 62.—Section through the kidney from which the isolated cysts shown in figure 59 were obtained. The "tubular" appearance of these cysts in histologic section is shown at the upper left hand part of the field.

None of the kidneys studied showed cysts whose size was sufficient to make them evident by gross examination. Even in the histologic section it was apparent that most of the so-called "microscopic cysts" were only sections through greatly dilated but continuous tubules, and

our descriptions of isolated tubules, in particular of the distal convolutions, show how enormous such dilatations may be. The occurrence of true cysts of small diameter can be certainly determined, therefore, only by the actual isolation of the dilated structures.

It is difficult to decide exactly what portions of the tubule contribute to the formation of these cysts. They lie in regions of the cortex or medulla that contain all the various portions of the tubule. Their epithelial lining, examined in section, is so simplified by atrophy that it no longer presents any evidence for identification, but from the appearances seen in figure 62 and in figure 38A of our previous study [9] one can at least be certain that both convoluted and "straight" tubules have been their source.

Besides cysts which contain within their walls a definite cavity, similarly rounded structures are found scattered through the areas of tubular disruption that are even smaller in diameter but entirely solid. Observed beneath a cover slip by higher magnification they are found to be clusters of plump, epithelial-like cells that frequently contain fat. Their situation among the products of tubular destruction and their rounded contours leave no doubt that they are masses of tubular epithelium in which no lumen persists.

Another form of tubular disruption, but one limited to a specific portion of the tubule, was also not recognized in our former study of this material by histologic sections. When the deeper layers of the cortex and the outer stripe of the outer zone of the medulla are dissected, among the hypertrophied and hyperplastic terminal spiral portions of the proximal convolution are found isolated segments of tubule the external contours and general configuration of which resemble exactly those of the intact enlarged kinked spiral (fig. 61). They are obviously interrupted or pinched off fragments of this terminal portion of the proximal convolution (fig. 60), for they may be found lying *in situ* arranged in a linear series, each unit closely following the other. The most distal of the isolated segments may continue into the narrow portion of Henle's loop (fig. 58).

In the dissection of these structures the greatest care was taken not to fracture a hypertrophic tubule and so produce artificial fragments. When isolated, each segment was carefully turned with the needles and examined at both ends for evidence of possible tearing or fracture. And to definitely establish that these objects are intact and independent structures, typical examples were removed from the suspending fluid, mounted on a slide beneath a cover slip and examined under high magnification. The pressure of the cover slip distorts their shape but has the advantage of flattening their contours. A photomicrograph shows that they are intact vesicles (fig. 63).

It is easy to see how such vesicles were unrecognized in histologic sections. Their contours are identical with those of the intact tubules among which they lie, and their epithelium, as can be seen by the thickness of their wall, is not atrophied, so that a section passing through them may differ in no essential way from one through a hyperplastic tubule that has maintained its normal continuity and that passes in and out of the section on its undulating course. We believe that even with serial sections one could decide only with considerable uncertainty whether or not a linear series of vesicles were connected.

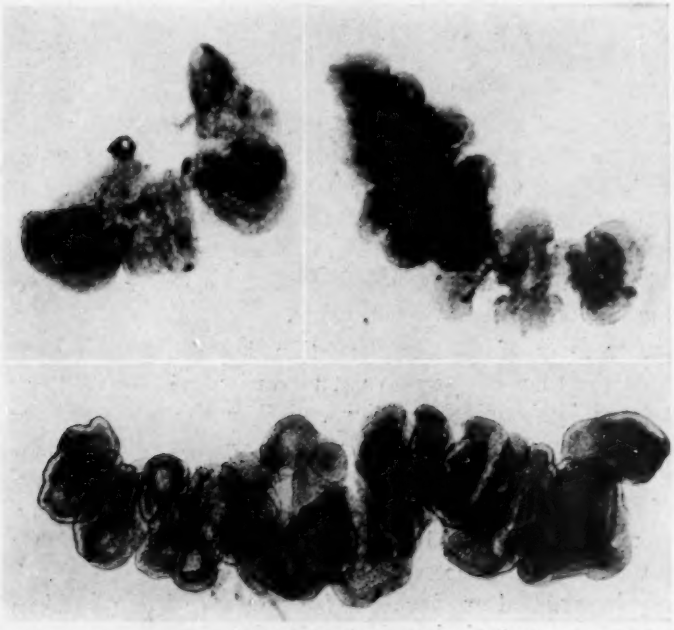

Fig. 63.—Three isolated vesicles similar to those shown in figure 61. The vesicles are shown by transmitted light at high magnification. Note that they are not artificial fragments but intact structures.

Since we have observed the effect of disruption at the junction of glomerulus and tubule and have seen the result of multiple interruption of the latter, it follows that the possibility remains of a single interruption occurring at some point in the tubule's course and this distal detached portion persisting more or less morphologically intact and unaffected. Such a structure would constitute an aglomerular tubule.

In the first study of this series a virtual aglomerular tubule was described and the significance of its occurrence noted. A fibrosed and therefore functionally absent glomerulus was attached to a hypertrophic tubule rather than to the collapsed and atrophied structure that has been presumed to follow glomerular obliteration. At the present time we

shall note only the occurrence of completely detached tubules; a detailed consideration of their structure with their relations to the detached glomerulus and blood vessels as illustrated by examples of actual isolated tubules and by reconstructions in models will comprise the third article of the present series. It is sufficient therefore to state that among the hypertrophied and hyperplastic terminal portions of the proximal convolution one frequently finds examples of these tubular segments completely cut off from their more proximal portion. The distal portions are morphologically well preserved in all detail and may continue uninterrupted, showing no unusual distortion or irregularity in their course (fig. 58).

COMMENT

If one considers the infinite modifications that are possible when pathologic processes including all the phenomena of degeneration, hyperplasia, hypertrophy and inflammation act over the course of years on a unit of such anatomic complexity as the nephron, it becomes evident that our description of the results of this first application of the method of microdissection to the problem of abnormal renal architecture makes no pretense at completeness. We believe that the more important of the typical alterations that occur in the nephron as a result of hemorrhagic Bright's disease have been described. Further study will supplement these observations, especially when the topographic relations of the abnormal nephrons are examined in the "contracted kidney."

Already certain new relations developing in the structure of the kidney as an organ have become apparent, for example, the mechanism of the shift in the circulation which long has been recognized, more, however, because its occurrence was demanded by logical considerations than because of exact objective demonstration. It is easily recognized by dissection that the isolated efferent vessels from the glomeruli are decreased in size, while Ludwig's vessels, normally so obscure that few observers have seen them, are found to be prominent structures as large as the afferent arteriole. The actual pathway of the blood stream as it is shunted past the obliterated capillary bed of the glomerulus can therefore readily be demonstrated. A further consideration of the details of these alterations in the blood flow will be given in the following article of this series in which the changes that occur in the tubule after glomerular obliteration will be described.

Another structural change in the abnormal organ is the occurrence of nephrons of a type not normally found in the human kidney. This change concerns the situation of the bend of Henle's loop, which always lies in the broad ascending segment in the short loops of the normal human kidney, though in the rabbit short loops may be found in which the bend is situated in the narrow segment. We have seen that when extreme hyperplasia occurs in the terminal portion of the proximal

convolution this structure not only kinks on itself as its cells increase in size and number, but also extends down deeper into the medulla. The thin segment of Henle's loop that formerly preceded it may be actually passed by the growing terminal segment of the proximal convolution and in fact be drawn after it as the hyperplastic tube advances. Consequently, the bend of the loop now lies in the narrow limb as in the nephron of the rabbit, and in some examples is situated at the immediate end of the proximal convolution.

Even more important general structural alterations result from tubular disruption, but a consideration of these will be reserved for the end of this section.

In the past there has been an inclination to think of the changes that occur in the nephron in Bright's disease as the result of a unit responding to general abnormal conditions. The tubule as a whole, or at least a complete division of it, is said to collapse when the glomerulus is destroyed, to hypertrophy when certain functional demands are thrown on it or to dilate when obstructed, or its epithelium is thought to undergo atrophy, degeneration, or death when adversely affected. Our examination of the entire nephron shows that this is not necessarily so. Fatty degeneration is frequently seen in the contiguous coils of a tubule cluster and these, when straightened out, show that only short segments, separated by normal-appearing epithelium, are involved. It is obviously a sharply localized factor that operated in such an instance, perhaps anoxemia due to the obliteration of a minute vessel, for no such effect is noted in the tubule as a whole. Similarly localized effects resulting from the pressure of connective tissue are seen alternating in the course of a single nephron. For example a large glomerulus is followed by an atrophic tubule which, as it passes to another region of the kidney, becomes hypertrophied and hyperplastic. Then extending to another area it returns to normal caliber and appearance, finally dilates and may repeat again almost any conceivable train of variation in its extended course through the diseased organ. In such cases one cannot speak of an "atrophic tubule" or of a "hypertrophied tubule." And since it is the nephron as a complete entity that is responsible for proper and complete function, the complications introduced in attempted correlation of structure and function by this variation within the unit are obvious and disconcerting. But a consideration of these difficulties can at least be postponed until the topographic problem of the abnormal kidney has been examined.

The importance of the proximal convolution is well established in the modern theory of renal activity. The observations in this study emphasize its paramount significance in the abnormal organ.

Only in the proximal convolution were progressive changes definitely observed. In this segment hypertrophy and hyperplasia were marked,

in fact, extreme, while all the other divisions of the tubule showed only changes of a passive or regressive nature, such as dilatation or fatty degeneration.

Especially prominent is the alteration seen in its terminal portion, the "spiral" of Schachowa and Schweigger-Seidel, an observation which correlates interestingly with the experimental deductions that from Ribbert and Susuki down to Richards in the present day suggest that various portions of the proximal convolution may have varying functions. So resistant, and, if one dare venture the word, so essential are these terminal portions of the proximal convolution that they persist as recognizable units even in the midst of the most disruptive of the disease processes. Vesicular structures and aglomerular tubules derived from them, still presenting evidences of vitality and progressive alteration, will be considered later.

The increase in length of the proximal convolution by the development in its terminal portion of hyperplastic kinkings and actual growth extension is a factor which has not previously been adequately recognized. In a previous study [1] the length of that portion of it which lies in the periglomerular cluster of loops was found by actual measurement of a reconstructed example to be 1.7 times the length of an average proximal convolution of the normal kidney. It was estimated therefore that, considering volumes, a hypertrophic unit of the terminal stage of the disease might replace, in physical size at least, six normal units. This estimate now needs correction, for the degree of the hyperplastic change in the terminal portion of the convolution was not recognized at that time. We now find that the hyperplastic terminal spiral may be equal in length to the periglomerular clustered portion, so that our former figure compared only one half of a possible hypertrophied proximal segment to the figure given by Peter for the entire normal convolution. The original length in our model of a complete hypertrophied convolution of 2.46 cm. may therefore be increased to 4.92 cm., and such an increase in length would double the volume. Our original statement should be amended to read that the hypertrophied unit may replace in physical size twelve normal structures. A considerable addition to the bulk of the persisting renal parenchyma is thus made by the hypertrophic and hyperplastic processes in the terminal portion of the proximal convolution.

The degree of hypertrophy and hyperplasia that have been noted in the proximal convolution and particularly in its terminal portion is a striking phenomenon, for nothing approaching the complex structural change that they produce has ever been noted in experimental studies of compensatory renal hypertrophy.[10] An explanation for this

10. Oliver, J.: Arch. Int. Med. **34**:258, 1924. Peters, E.: Ztschr. f. Zellforsch. u. mikr. Anat. **8**:63, 1928.

fact may possibly be found in the difference in the nature of the blood that supplies the tubules in a normal kidney undergoing compensatory hypertrophy after unilateral nephrectomy and that which circulates through the kidney in the terminal stage of hemorrhagic Bright's disease.

In the former case, the proximal convolutions of the tubule that are undergoing hypertrophy receive blood that has passed through the glomerulus and has therefore undergone whatever changes of elimination normally occur in this passage. Moreover, the glomeruli increase in size and presumably become more effective. The added burden that produces the hypertrophy of the tubule cells is therefore contained in blood that has been at least partially purified by the normal glomerular eliminatory procedure. In this instance tubular hypertrophy may be looked on as largely compensatory for tubular inadequacy.

In terminal Bright's disease, however, the greater part of the blood that reaches the proximal convolution has not undergone change by a passage through the glomerular mechanism, for it has been shunted directly by Ludwig's vessel to the tubule cells. Consequently they are burdened not only with products that have accumulated because of the destruction of other tubules, but by the added demand that results from glomerular destruction and insufficiency. In this instance tubular hypertrophy is compensatory for both tubular and glomerular inadequacy, and it might therefore be expected to assume unusual proportions. Further and even more direct evidence of the ability of the tubules to take over the function of the progressively decreasing glomeruli will appear in our next study.

Of equal importance with those active processes in the nephron that transfer waste substances from the blood into the lumen is the passive action of drainage by which the lumen is cleared of the products of elimination. The present study emphasizes the impedance to this drainage that develops in the abnormal kidney, for it illustrates the frequency and extent of the interference and shows the exact method and points in the nephron where obstruction is most apt to occur. It must be remembered that the only kidneys available for study were those that had failed completely, since they were selected from the terminal stage of the disease. The failing circulation and the consequent diminution in the flow of urine in the last few hours of life doubtless exaggerated some of the appearances noted, but other evidences are seen of obstruction of such long standing as to have caused permanent structural change in the tissues.

The simplest obstructing mechanism observed was the plugging of the lumen of the nephron with solid matter. Two distinct kinds of occluding material were observed, and these under conditions that indicate an entirely different significance. One substance is homogeneously

clear and translucent; the other is a heterogeneous mixture of granular detritus of varying density that is often mixed with droplets of fat. Associated with obstruction by either sort of material is found dilatation of the tubule, an occurence which precludes the possibility that either might be a simple precipitation from albuminous urine by the action of the solution of formaldehyde or the acid. If in certain cases the dilatation is only moderate, it must be remembered that one of the well established functions of the tubule is the absorption of water, and this would be favored by the increase in pressure produced by the occlusion of the lumen.

The heterogeneous fatty granular material has all the appearance of débris that has been swept by the current of the urine from higher levels of the nephron to collect in certain traplike parts of the course of the tubule. It is found at tortuous or kinked points, particularly in the distal convolution and in the loops of the peripheral or in the abnormal deformities of the central collecting tubules. When found elsewhere it can be followed along the course of the tubule more or less continuously to one of these occluded points, an appearance which indicates that it has extended back by accumulation. This interpretation of an accumulation over a period of time is further supported by the stuffed appearance of the tubule with its irregularly bulging local dilatations and by the laminations and irregularities of density and of fatty admixture that build up the contents of the occluded tubule.

The clear translucent substance, on the other hand, is never limited to a definite restricted segment of the tubule but extends through long stretches, at times including an entire peripheral collecting tubule, the connecting piece, the distal convolution and the broad limb of Henle's loop. The entire length of the tubule is greatly and uniformly dilated, and its contours are rounded by an evenly distributed internal distention. The appearance is that of a marked dilatation with fluid that has collected behind an obstruction and then coagulated *en masse* at a given time. The actual obstruction may be the granular débris previously described. With such an interpretation the time of coagulation may have been either ante mortem or post mortem without affecting the significance of the result, since the obstruction is the essential matter.

None of the solid masses so far described comprise the casts that are found in the bladder urine. Obviously no mold of the lumen of the proximal convolution that approximates in diameter that of the typical urinary cast could pass through the narrow limb of Henle's loop, nor does it seem likely that one from the ascending limb could make its way through the complex and acutely bent kinks of even a normal distal convolution. This division in itself contains no sufficiently straight portions in which a urinary cast could be formed, and, as a matter of fact, no typically formed casts are ever seen in these upper reaches of

the tubule. It follows therefore that all those found in the bladder urine must be derived from the peripheral and central collecting tubules, though the material from which they are formed, whether débris, albuminous substances, desquamated epithelial cells, leukocytes or red blood cells, may be derived from any portion of the tubule, provided its lumen is not obliterated.

Typical straight well formed hyaline or granular casts with rounded ends were seen in all the collecting tubules. Since the course of these is direct and their lumens increase in size with their progression through a kidney the structure of which has not been greatly altered, their passage into the bladder urine is a simple matter. The only possible obstructions are the loops that occasionally occur in the course of the peripheral collecting tubules.

In the kidney whose structure has been altered, however, the fusiform segmented deformity so frequently observed in the central collecting tubules prevents the further passage of casts toward the pelvis of the kidney. As such deformities increase in number with the progress of the disease, and as heterogeneous débris clogs the irregularities of the larger ducts, the number of casts from the smaller peripheral collecting tubules must decrease. Only those formed in the terminal central ducts can enter the bladder urine. And in this fact a simple explanation is found for a clinical observation that has previously been obscure. In the last period of the terminal stage of the disease Addis has noted an increase in the size of the casts found in the urine.[11] Both the number of the larger casts and their average diameter increase progressively until their size approximates that of the ducts of Bellini. In the "cast count" of such a case the large renal failure casts rise to 100 per cent, while the percentage of hyaline and other casts of usual diameter falls to 0. It is evident that what occurs is a progressive clogging of ever larger collecting tubules, and that although this obstruction allows urine to filter through, it holds back the formed casts from the smaller tubes.

Obstruction affects in no small way the course of the structural changes in the terminal stage of the disease, and the final effects of many of these alterations are determined almost entirely by such "hydronephrotic" factors. And such effects are cumulative, for a vicious circle is soon established in which clogging and obstruction, as they produce stasis in the flow of urine, favor increased accumulation of débris. The permanency of such obstruction of the tubule by débris is hard to determine, but the inert substances as they are seen in the densely packed rigidly deformed distal convolutions and in the stuffed segments of the larger fusiform collecting tubules have an appearance of remarkable solidity and finality. Urine must be seeping past or through the occlud-

11. Addis, T.: J. A. M. A. **84**:1013, 1925.

ing material, and it may be that in this way there results a certain disintegration of the distal end of the occluding mass, but a never ending source of supply for new accumulation is always present in the degenerating nephron above.

Interference with proper drainage is the obvious functional disturbance produced by the obstructive accumulations. That the more complex functional activities of the organ are affected in a deleterious manner seems equally certain, even if the exact nature of these disturbances is less clear. Back pressure would militate against excretion of both water and solids, whether they are eliminated by filtration or by secretion, while absorption of water or substances like urea might be exaggerated.

Obstruction to the flow through the nephron may also follow an actual interruption of the tubule by the pathologic reactions of the disease, and a result of these disruptions is the production of structures that have no analogies in the normal kidney. When the tubule is surrounded by inflammatory tissue it is compressed, and in the late stages when a dense collagenous scar is forming it may ultimately be pinched off completely. A nephron ending blindly is thus formed, which dilates with its accumulating excretion. Such an interruption may occur at any point of the nephron and is irreparable. Repeated interruptions of this kind also are found in the course of a single nephron. When the hypertrophic and hyperplastic terminal portion of the proximal convolution is involved a series of completely closed vesicles is formed the irregular contours of which retain the characteristic appearance of the original hyperplastic tubule.

Even more frequent is the multiple interruption of tubules of normal caliber. Since an area of scar tissue may be extensive, a great number of tubules may be thus included throughout a considerable stretch of their course, and the final effect is a mass of clustered small round cysts the diameters of which are equal to that of the original tubules.

Such vesicles and cysts are, of course, functionless and in certain cases may comprise a considerable part of the epithelial-tubular element of the diseased organ. Their recognition is therefore important when any attempt is made at correlation of structural change and functional ability. In the ordinary histologic preparation, however, both vesicles and cysts have in cross-section an appearance almost identical with that of the tubule from which they are derived. In looking over our earlier histologic descriptions of these same kidneys we have found these worthless cysts described as "tubules." Such an interpretation, whatever functional activity might have been assigned to the tubules, considers them at least capable of transporting urine. In the light of this dis-

crepancy, it is not surprising that correlation of structure and function has been inadequate when, as in the past, it was made solely by the study of sections.

Another result of the disruption of the nephron is concerned with the persistence of portions of the proximal convolution as independent structures which do not of necessity atrophy or collapse. They have been found not only to persist but to show the active progressive changes of hypertrophy and hyperplasia. They constitute in a very strict sense aglomerular tubules and will form the subject of the next study of this series.

LIGATION OF THE COMMON BILE DUCT IN THE RAT

ANATOMIC AND BEHAVIORISTIC EFFECTS

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Previous papers from this laboratory have reported experiments in which an attempt was made to study the rôle played by various organs of the body in the production and regulation of spontaneous activity. In brief, the object of these experiments was to determine what makes an animal active, how it can be made chronically overactive (experimental mania), how it can be made chronically inactive (experimental depression) and finally how it can be brought back to normal again, once these abnormal states of activity have been produced. It is hoped that with knowledge thus obtained of the principles underlying activity in animals, some light may be thrown on the origin and control of abnormal states of activity in man.

One approach to this problem has consisted of an attempt to determine the effect produced on activity by removal of various organs of the body. In this way it has been found that the endocrine glands play a particularly important rôle, since removal of the gonads, hypophysis, suprarenals or thyroid results in a great permanent drop in activity. In marked contrast, removal of the pineal gland, salivary glands, thymus, spleen, uterus, seminal vesicles or prostate produces no change in activity (Richter [1]).

As a part of this survey we have investigated the liver, because of its recognized function of regulating metabolism and the general energies of the body. Owing to technical and vital physiologic difficulties it was thought best not to extirpate the liver but rather to be content at the outset with a study of the effects produced on activity by a marked alteration in its function, leaving it in situ. The most obvious procedure was to study first of all the effect produced by ligation or actual transection of the common bile duct. By this operation the channel through which the secretions from the liver pour into the intestinal tract is closed, while the connection between the liver and the blood stream is still intact.

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1. (*a*) Richter, C. P.: Quart. Rev. Biol. **2**:307, 1927; (*b*) Am. J. Orthopsychiat. **2**:345, 1932.

These experiments have brought out certain relations between the liver and spontaneous activity, but of even greater interest are the amazing anatomic changes produced by ligature of the bile duct, not only in the liver but also in the bile duct itself.

METHODS

The technic followed in measuring the activity of the rats has been described in detail in a previous paper (Richter [18]). Each animal was kept in a separate cage containing a revolving drum and a living compartment, with a food cup and water bottle. The animals had free access to the revolving drum, the revolutions of which were recorded on a cyclometer. Activity and the intake of food and water were recorded daily and the animals were weighed once each week.

Twenty-four animals were used in these experiments. They were placed in the cages at the usual age, between 35 and 45 days, but the bile ducts were not ligated until several weeks later, when a fairly high running level, approximately 6,000 to 8,000 revolutions per day, was attained. The age at the time of the operation varied from 41 to 164 days.

The operative technic was simple. Under ether anesthesia a 2 inch (5 cm.) midline incision was made in the abdominal wall beginning just below the sternum and exposing the liver and stomach. It was found that the exposure could be greatly improved by placing silver retractors so that they pulled the walls slightly upward as well as outward. A small silver retractor covered with cotton was inserted into the incision from the anterior end and hooked under the liver, so as to make an opening between the liver and the stomach and thus expose the common bile duct clearly to view.

In some of the animals the duct was tied with a single silk ligature and left unsevered; in others it was tied off with a double ligature and transected between.

At autopsy the abdominal organs were subjected to careful gross examination, and the glands of internal secretion and the brains were removed for histologic study. The liver was fixed in a diluted solution of formaldehyde, U. S. P. (1:10) embedded in paraffin, sectioned at 10 microns and stained with hematoxylin and eosin.

RESULTS

Effect on Activity.—Ten of the twenty-four animals became markedly inactive after the ligation of the common bile duct (group I). The remaining fourteen either showed no effect, or, after a short period of inactivity, became as active as normal animals and, in a few instances, even more active (group II).

Two typical records from animals of the inactive group are presented in figure 1, in which the running activity, expressed in the number of revolutions of the drum, is indicated on the ordinates and the age of the animal in days on the abscissas. The animal represented at the left became totally inactive after the bile duct was ligated, its activity dropping from a level of over 8,000 revolutions per day to less than 100. Death occurred fifty days later. The animal represented at the right also was totally inactive at the time it died, fifty-four days after the ligation of the duct. In contrast to the first animal, however, it remained fairly active for fifteen days after the ligature was applied.

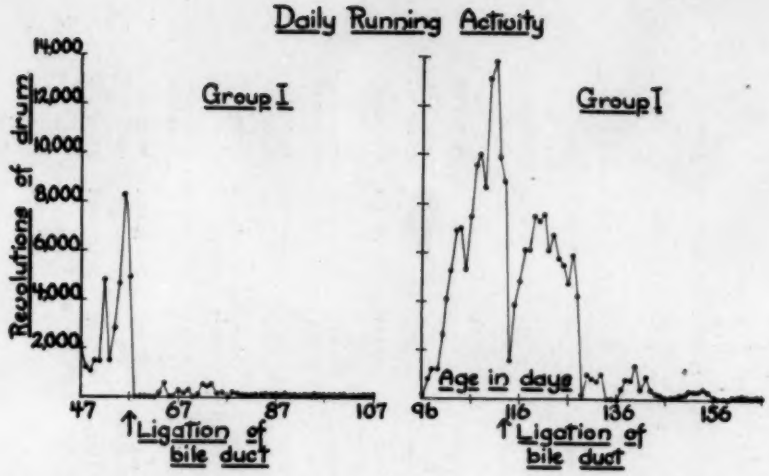

Fig. 1.—Effect produced by ligation and cutting of the bile duct on the running activity of animals in group I.

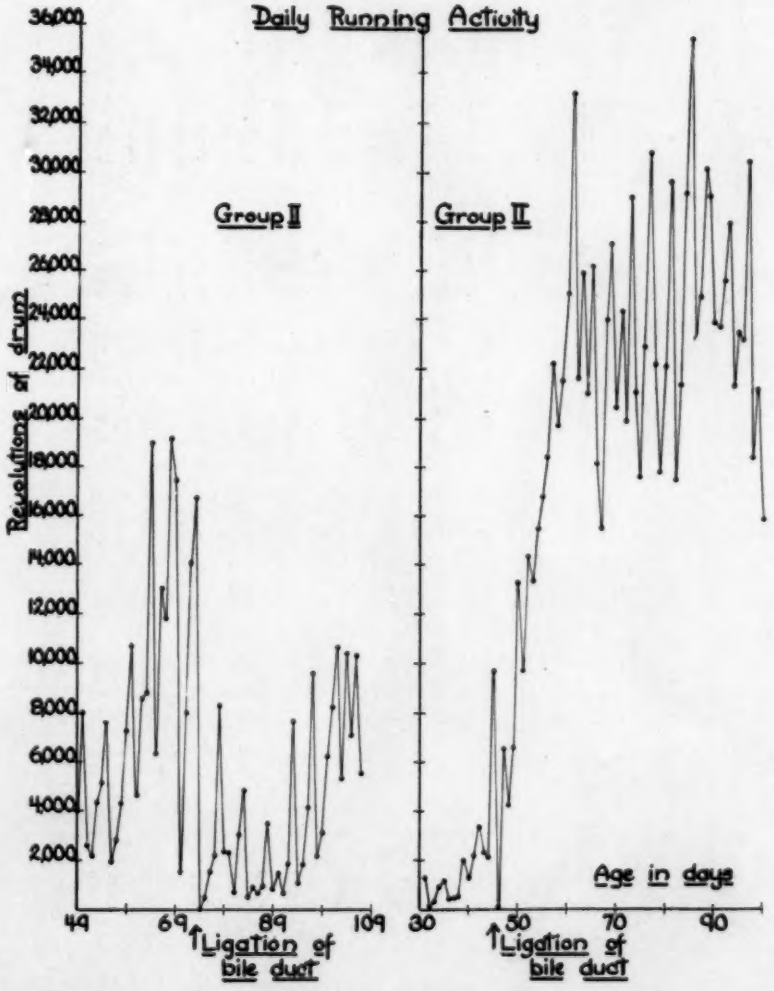

Fig. 2.—Effect produced by simple ligation of the bile duct on the running activity of animals in group II.

Experimental Records of Animals in Groups I and II

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
					Average Activity*				Liver					
Rat	Sex	Age at Operation, Days	Length of Life after Operation, Days	Position of Ligature	Ten Days Before Operation	Last Five Days of Life	Retroperitoneal Fat	Dilatation of Common Bile Duct	Degree of Biliary Cirrhosis	Degree of Biliary Necrosis	Proliferation of Bile Canaliculi	Degree of Fibrosis	Bile Duct	Status of Pancreas on Gross Examination
Group I														
118C	F	57	55 (died)	Double ligature and cut	2,971	13	Entirely gone	Very marked	Very marked	Very slight	Very marked	Slight	Not patent	Atrophied
140C	M	138	16 (died)	Double ligature and cut	5,037	493	Entirely gone	Very marked	Very marked	Marked	Very marked	Slight	Not patent	Slightly atrophied
20C	F	86	20 (killed)	Double ligature and cut	11,467	635	Entirely gone	Very marked	Very marked	Very slight	Very marked	Very slight	Not patent	Markedly atrophied
329B	F	114	59 (killed)	Single ligature near liver	4,895	4	Entirely gone	Very marked	Marked	Very slight	Very marked	Slight	Not patent	Atrophied
345B	F	114	55 (killed)	Single ligature near liver	9,217	24	Entirely gone	Very marked	Very marked	Marked	Very marked	Very slight	Not patent	Markedly atrophied
282B	F	164	44 (died)	Single ligature near liver	14,100	197	Entirely gone	Very marked	Very marked	Moderate	Very marked	Very slight	Not patent	Markedly atrophied
127C	F	41	40 (died)	Double ligature and cut	8,346	569	Markedly decreased	Slight	Marked	Very slight	Very marked	Very slight	Not patent	Normal
374B	F	51	31 (killed)	Single ligature near duodenum	7,771	1,964	Entirely gone	Very marked	Very marked	Very slight	Very marked	Slight	Not patent	Markedly atrophied
123B	F	44	29 (died)	Double ligature and cut	1,915	431	Entirely gone	Very marked	Marked	Very marked	Very marked	Moderate	Not patent	Markedly atrophied
144B	F	47	35 (died)	Double ligature and cut	6,214	1,181	Entirely gone	Very marked	Marked	Marked	Marked	Slight	Not patent	Atrophied
Average (for 10 rats)			37		7,193	551								

Experimental Records of Animals in Groups I and II—Continued

Group II														
364B	F	50	33 (killed)	Single ligature near liver	3,094	5,816	Slightly decreased	None	Slight	None	Slight	None	Patent	Normal
375B	F	110	68 (killed)	Single ligature near liver	14,572	16,177	Normal	None	Slight	None	Very slight	None	Patent	Normal
26C	F	46	60 (killed)	Single ligature near liver	2,143	11,826	Normal	None	Slight	None	Slight	None	Patent	Normal
50C	F	42	29 (killed)	Double ligature near duodenum	9,695	10,307	Slightly decreased	None	Slight	None	Moderate	Very slight	Patent	Normal
254B	F	121	86 (killed)	Double ligature near duodenum	15,796	6,654	Slightly decreased	None	Slight	None	Slight	Very slight	Not patent	Normal
347B	F	74	34 (killed)	Single ligature near duodenum	12,468	7,746	Normal	None	Slight	None	Slight	None	Not patent	Normal
39C	F	49	60 (killed)	Single ligature near liver	4,934	4,457	Slightly decreased	Slight	Slight	None	Moderate	Very slight	Patent	Atrophied
330B	M	141	33 (killed)	Single ligature near duodenum	5,727	1,349	Slightly decreased	None	Slight	None	Moderate	Very slight	Not patent	Normal
35C	F	46	38 (killed)	Single ligature near liver	1,684	1,847	Normal	Slight	Slight	None	Slight	None	Patent	Normal
42C	F	41	40 (killed)	Single ligature near duodenum	1,877	5,703	Decreased	None	Slight	Slight	None	None	Not patent	Normal
38C	F	45	60 (killed)	Single ligature near liver	2,195	18,182	Moderately decreased	Slight	Slight to moderate	None	Moderate	Very slight	Patent	Slightly less than normal
341B	F	57	52 (killed)	Single ligature near liver	12,423	10,886	No autopsy notes						Not patent	
361B	F	50	40 (killed)	Single ligature near liver	15,235	12,301	Very slightly decreased	None	Slight	None	Moderate	Very slight	Patent	Normal
363B	F	50	33 (killed)	Single ligature near liver	11,101	10,985	Slightly decreased	None	Slight	None	Moderate	Slight	Patent	Normal
Average (for 14 rats)					8,069	8,874								

* Expressed in number of revolutions on the drum.

The curves in figure 2 were obtained from the active group. The animal whose record is shown at the left was inactive for about ten days after the operation but was rapidly approaching the original high level of activity when it was killed thirty-four days afterward. The animal whose record is presented at the right showed no initial depression after the ligature of the bile duct, but became more active at once, finally reaching a level of about 28,000 revolutions per day, which is considerably above the normal average. It was killed fifty-five days after the operation.

The results of these experiments are summarized in the table, the scheme of which is self-evident. The records for the ten animals of group I are given at the top of the table, those for the fourteen animals of group II below.

In the sixth and seventh columns it will be seen that the average activity of group I dropped from 7,193 revolutions per day to 551, while that of group II increased from 8,069 revolutions per day to 8,874. An inspection of the individual records of the animals of group I shows, moreover, that every animal became much less active after the ligature of the bile duct. One animal averaged only 4 revolutions per day, whereas some of the animals of group II averaged as high as from 16,000 to 18,000 revolutions.

It will be noted in the fourth column that the six animals of group I that were not killed died from sixteen to fifty-five days after the ligature was made, or after an average of thirty-six days, whereas none of the animals of group II died. There is little reason to doubt that the other four animals in group I would have died at about that time had they not been killed.

The fifth column discloses the noteworthy fact that all of the six animals in which the duct was cut as well as ligated fall into group I. Otherwise, the type and position of the ligature, whether single or double and whether nearer the liver or nearer the duodenum, seem of no importance in separating the groups.

Effect on the Liver.—At autopsy marked organic differences, both macroscopic and microscopic, were observed in the animals of the two groups. These data are summarized in columns 8 to 15 inclusive of the table.

In all of the animals of group I a marked dilatation of the common bile duct was noted. This duct, which in the normal animal is scarcely larger than a small thread, had dilated so much that in some cases it almost filled the entire abdominal cavity (fig. 3). Three of the animals of group II showed a very slight dilatation of the duct, the others none.

The patency of the bile duct was tested by means of injections of india ink made at the point at which the bile duct enters the duodenum and at which it leaves the liver as the common duct. It was noted that

in nine of the animals of group II the ink went through the duct, whereas in all of the animals with the marked dilatation (group I) it did not.

The retroperitoneal fat had entirely disappeared in all but one animal of group I and in this it was markedly diminished. In group II, on the other hand, the deposit of fat was essentially normal. Histologic study of sections of the liver revealed a striking biliary cirrhosis with some necrosis, marked proliferation of the bile ducts and general diffuse

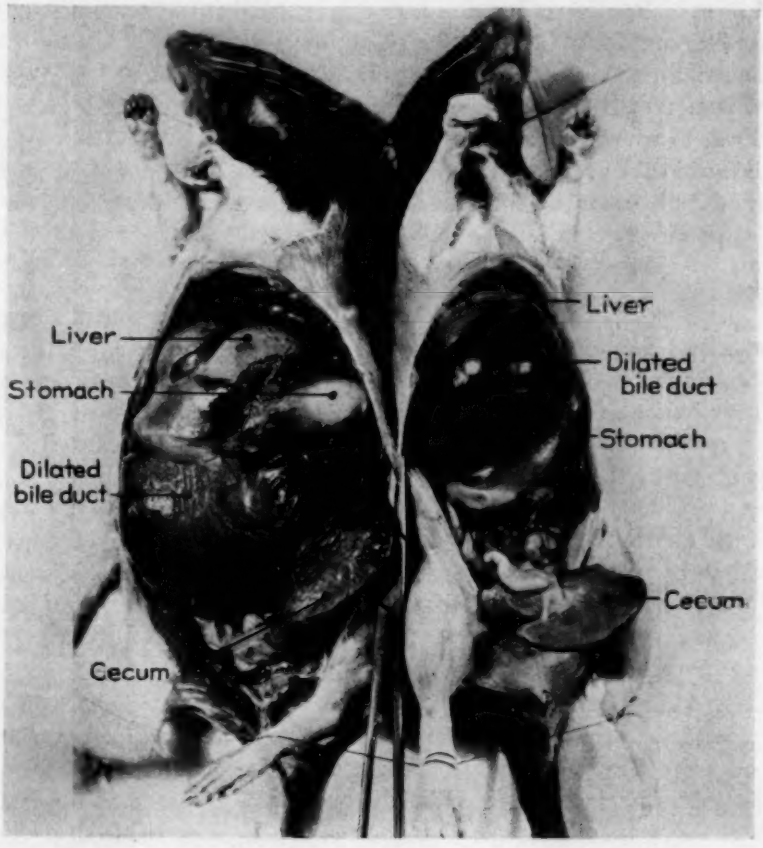

Fig. 3.—Two rats with markedly distended bile ducts.

periductal fibrosis (columns 10 to 14 in the table). In the animals of group II there were only very slight cirrhosis and necrosis and slight proliferation of the bile duct and fibrosis.

In the fifteenth column of the table it will be seen that the pancreas was atrophied in all but one of the ten animals in group I, and in only one of the animals of group II. In several cases the atrophy was striking.

In summary it may be said that in the animals of group I made inactive by successful ligation of the bile duct, a damming up of bile caused a marked dilatation of the common duct, with widespread destruction of liver cells, marked cirrhosis and proliferation of the small bile canaliculi or ducts together with a complete disappearance of the retroperitoneal fat and an atrophy of the pancreas. In the animals of group II, with an unchanged or heightened curve of activity, the secretion of bile escaped through the normal channels provided by the regenerated bile duct. The slight alteration in the liver noted in these animals must have been produced during the short interval after the ligation and before the new channel had been formed.

These results confirm the observations of Cameron and Oakley,[2] in 1932, to which our attention has recently been drawn. The changes described in the present series are somewhat more pronounced, however, since the dilatation of the bile duct was greater and the alteration in the liver more marked.

COMMENT

These experiments were undertaken to determine whether changes in the liver resulting from ligation of the bile duct have any effect on spontaneous activity. The purposes of the experiment were defeated in over half of the animals by the unexpected regeneration of the bile duct, and in the others the conditions were much complicated by the appearance of the large dilatation of the bile duct, which in itself might have a profound effect on activity. Thus it became difficult to determine to what extent the marked inactivity of the animals in the latter group could be ascribed to the changes in the liver following the blocking off of the normal channels of escape of the bile, or to the mechanical pressure exerted by this large sac on the various internal organs as well as on the general circulatory relationships.

The bulk of the evidence favors the view that the changes in the liver with the probable presence of bile salts and acids in the circulating blood were the primary factors, since in almost every instance the animal became inactive immediately or within a few days after the ligation, long before the bile duct had reached an appreciable size.

An attempt was made in four animals to settle this question by means of a fistula of the bile duct. The idea was to determine whether animals made inactive by ligation of the bile duct become normally active again by permitting the bile in the sac to drain off freely to the outside through a fistula. The operative difficulties did not make it possible to settle this question. All of the animals died of abdominal hemorrhages resulting from the release of pressure after the saccular bile duct was opened to produce the fistula. It may be mentioned that particular care was used to make

2. Cameron, G. R., and Oakley, C. L.: J. Path. & Bact. **35**:769, 1932.

the escape of fluid very gradual in order to avoid a sudden drop in abdominal pressure. The slight release in pressure from a small incision in the abdominal wall apparently is sufficient to produce fatal internal hemorrhages. However, as before stated, the rest of the evidence seems to indicate that the inactivity is not produced by the dilatation but by the changes in the liver.

The nature of the mechanism through which this inactivity is produced is not clear. It seems likely, however, that the damming up of the bile and its consequent forced injection into the blood stream in abnormally large quantities may be an important factor. This is suggested particularly because of the work of Crandall and Weil [3] in which it was shown that the bile acids had a destructive action on the nerve tissue in rats, and further that ligation of the common bile duct in dogs produced widespread atrophy of the tissue of the brain, particularly of the lenticular nucleus. Such great destructive changes in the brain tissue might easily account for the marked inactivity. However, against this possibility several facts can be offered: First, the rats do not show definite jaundice, except when the bile duct ruptures, and second, the animals become inactive within the first few days after the ligation, whereas, according to Crandall and Weil, no histologic changes appear in the brain of the rat until from four to eight weeks later. In agreement we noted no detectable histologic changes in the brains of six of our animals killed three weeks after the ligation of the bile duct.

We hope to be able to throw light on this problem by further experimentation on the effect produced on activity by injection or feeding of bile acids and salts.

An attempt also was made to find some explanation for the increased activity of a few of the animals of group II in which the bile duct had regenerated after the suture. It occurred to us that in these animals the ligation might in some way have made it possible for the liver to retain or store more glycogen and consequently have more energy available for running activity. However, stains for glycogen on sections from the livers of these and normal animals showed no appreciable differences.

SUMMARY

In twenty-four rats the common bile duct was ligated singly or doubly and then cut, and a study made of the effect produced on spontaneous running activity. An attempt was made to correlate these effects with histologic changes in the liver.

Ten of the animals became very inactive; fourteen either remained normally active or possibly became even hyperactive.

3. Crandall, L. A., and Weil, A.: Arch. Neurol. & Psychiat. **29**:1066, 1933.

All of the inactive animals showed striking changes at autopsy: The common bile ducts were markedly dilated, in some instances practically filling the entire abdominal cavity; the retroperitoneal fat was absent, and the pancreas atrophied. Histologically the liver showed a typical biliary cirrhosis with extensive sprouting of small bile ducts and necrosis.

The active animals showed a patent duct with slight or no dilatation, normal retroperitoneal fat and a normal pancreas. Histologically the liver showed slight biliary cirrhosis and proliferation of the bile canaliculi.

It was pointed out that several factors must be taken into consideration in explaining the inactivity produced by ligation of the bile duct—the mechanical effects of the presence of the large sac in the abdominal cavity, its pressure on the other organs and the chemical effects of the bile injected into the blood stream and acting particularly on the brain.

STUDIES IN ATHEROSCLEROSIS: CHEMICAL, EXPERIMENTAL AND MORPHOLOGIC

V. POSSIBLE DANGERS OF IODINE THERAPY IN ATHEROSCLEROSIS OF AORTA SEEN FROM AN EXPERIMENTAL STANDPOINT

SOL ROY ROSENTHAL, M.D., PH.D.

CHICAGO

The supposed action of iodine in atherosclerosis of the aorta is that of (1) healing by direct influence on the atheroma or by indirect influence on the intermediary cholesterol metabolism (Liebig, Hildebrandt, Abelin, Friedland), (2) increasing the functional discharge of blood from vessels and thus maintaining a better supply of blood to the organ (Guggenheimer and Fisher), (3) lowering the blood pressure (Potain and Thoussig) and (4) reducing the viscosity of the blood (Müller and Inada, Romberg).

All of these activities have been open to question experimentally. Thus Mancke, also Freund and König could not verify the work of Guggenheimer and Fisher, who described a widening of the coronary arteries after transfusing hearts with diluted solutions of iodine; Gumprecht, Stockman and Charteris, and Janeway found no decrease in blood pressure, while Blum (cited by Liebig) found that the blood pressure might be lowered or elevated. Brokling and von Boruttau (cited by Liebig) found no changes in the viscosity of the blood after the administration of iodine.

In support of the first hypothesis, Liebig was first to show that iodine in massive doses prevented atheromatous deposits in cholesterol-fed rabbits (later Turner), while Seel and Creuzberg reported that by using small doses of iodine not only could the deposit of lipoid in the aorta of the cholesterol-fed rabbit or guinea-pig be prevented, but after a steatosis had developed, it could be reversed by the administration of iodine.

The recent studies of Turner and Khayat show that iodine was not effective unless the thyroid gland was present. These authors allowed one to infer that the action of the iodine was an indirect one working through the thyroid gland.

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From the Pathologic Institute, Freiburg, Germany, Dr. L. Aschoff, director; the chemical division of the Pathologic Institute, Freiburg, Germany, Dr. Schönheimer, formerly director, and the Pathologic Institute of the Cook County Hospital Chicago, Dr. R. H. Jaffé, director.

That the thyroid gland played some rôle in the prevention of experimental atherosis of the aorta was shown by Murata and Kataoka, who prevented this state by the administration of thyroxine, and verified by Friedland and more recently by Turner. On the contrary, the removal of the thyroid gland hastened the development of atheromatous deposits in the aorta (Shapiro, Friedland). Whether the influence of the thyroid gland prevents absorption of cholesterol or increases excretion of cholesterol has not been demonstrated, but it is definitely known that with large doses of iodine, thyroxine or whole thyroid, the blood cholesterol in the experimental animal is diminished (Liebig, Turner, Turner and Khayat). The degree of atherosclerosis of the aorta in experimental animals is directly proportional to the level of the blood cholesterol (Anitschkow).

Unfortunately, in the studies of the action of iodine reported, the thyroid gland was not examined nor was the basal metabolic rate, so that the degree of activity of the thyroid gland cannot be stated. In the studies of the action of thyroxine Friedland showed that a definite increase of the basal metabolic rate as well as a loss of weight occurs. Abelin found as much as a 100 per cent increase of the oxygen requirement in mice fed thyroxine. Microscopic examination of the aortas of the animals fed large doses of thyroxine (Friedland) or iodine (Hedinger and Lach, cited by Liebig) showed severe medial calcification similar to the epinephrine type of sclerosis.

From an experimental standpoint it is suggestive that the action of iodine is determined by the activity of the thyroid gland and that although the deposits of lipoid are hindered when massive doses of iodine or thyroxine are administered, a severe medial calcification follows.

The question arises: What will large physiologic doses of iodine do toward the prevention of deposits of lipoid in the aorta of the cholesterol-fed rabbit? This problem has been elaborated on and will be discussed in later paragraphs.

METHOD

Rabbits of about the same age (1 year) were used. Except for two of the controls, all were fed, on the average, 0.5 Gm. of cholesterol dissolved in 10 cc. of linseed oil daily for about one hundred and twenty days. This substance was administered by the aid of a stomach tube. The regular diet of hay, oats and later turnips and grass was given in addition to the cholesterol.

Studies were made on the following groups: Group 1 (controls—subgroups *a* and *b*, 5 animals each) fed (*a*) cholesterol in oil plus the regular diet; (*b*) regular diet only. Group 2 (subgroups *a* and *b*. 5 animals each) fed (*a*) cholesterol in oil plus potassium iodide (at first 3 mg. of potassium iodide, equal to 2.15 mg. of iodine per day,

which was increased to 4.5 mg. of potassium iodide, equal to 3.37 mg. of iodine per day); (*b*) cholesterol in oil to which potassium iodide was added six weeks later (doses of potassium iodide same as in *a*). Group 3 (subgroups *a* and *b*, 3 animals each) fed (*a*) cholesterol in oil plus Jodtropon [1] (40 mg. of Jodtropon, equal to 2 mg. of iodine per day, which was increased to 66.5 mg., equal to 3.37 mg. of iodine per day); (*b*) cholesterol in oil to which Jodtropon was added six weeks later (doses of Jodtropon the same as in *a*).

Determinations of the blood cholesterol, free and combined, were made weekly, employing a newly devised method of Schönheimer and Sperry (not yet published) in which very small quantities of serum were needed (0.2 cc.). The principle involved in this method is similar to that in Windaus' use of digitonin for the precipitation of the cholesterol, but the determination quantitatively of the digitonin cholesterol precipitate is made photometrically using anhydrous acetic acid and concentrated sulphuric acid for the color formation. As no other reports on iodine gave the relations of the free cholesterol to the ester in the blood and because only one other report on cholesterol feedings gave these relations and that one to a limited degree (Wacker and Hueck), a more detailed description of these will be given. The blood cholesterol curves of only one animal of each group are given. Although there were variations in each group, the curves given show the general trend of each division.

CHOLESTEROL CHANGES IN THE BLOOD SERUM

Group 1 a (regular diet plus cholesterol in oil).—The total serum cholesterol increased slowly from a normal of 55 to 65 mg. per hundred cubic centimeters to double that much in the third week, then it sank to a little above normal and remained constant until the fifth week, when a sharp rise occurred extending over a period of from three to four weeks with the values soaring to an average of 900 mg. per hundred cubic centimeters. From then on a sharp fall for about three weeks was noted, then again a rise, then a fall, and finally a gradual rise by a stepladder type of ascent to 1,400 mg. per hundred cubic centimeters.

The relationship of free cholesterol to cholesterol esters, which normally varies from 35:65 per cent to 25:75 per cent, attained a high normal value averaging 26:74 per cent. For short periods (one week) an increase of the cholesterol ester to 80 per cent or slightly over occurred (fig. 1).

Group 2 a (regular diet plus cholesterol plus potassium iodide).—The total serum cholesterol increased very rapidly and at the end of the third week reached on the average 500 mg. per hundred cubic centi-

1. Jodtropon is an organic iodine bound intramolecularly with protein. It is manufactured by the Troponworks Dinklage & Co., Cologne-Mühlheim, Germany.

meters. In the following week it fell to about twice the normal value, while in the next five weeks a very acute rise took place, reaching 2,500 mg. per hundred cubic centimeters (the low value was 1,600 mg.). A slight drop followed for a week or two and then again a high level was attained.

The percentage of cholesterol ester was somewhat above the high normal with an average of 78 per cent (fig. 2).

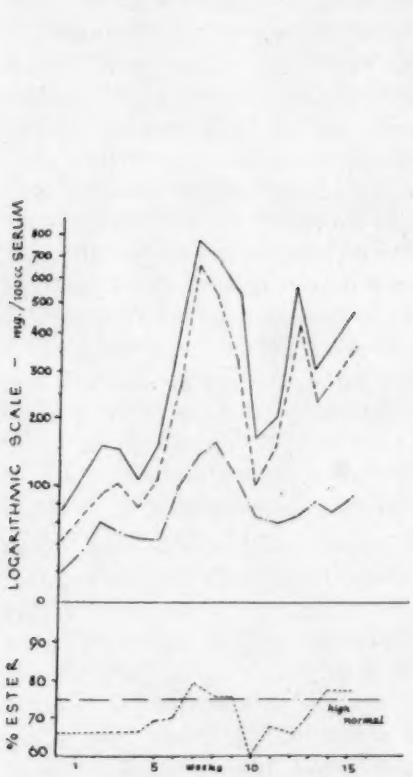

Figure 1

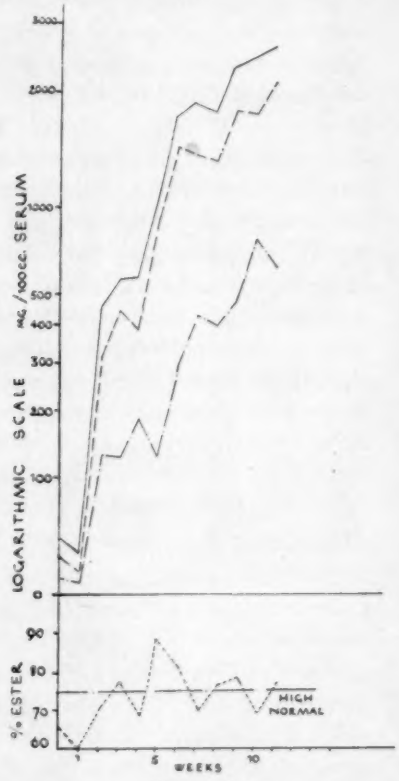

Figure 2

Fig. 1.—Cholesterol changes in the blood serum of a representative rabbit (83) of the control group 1*a* which had cholesterol in oil added to the regular diet. In all the charts the total cholesterol is represented by an unbroken line; cholesterol ester, by a line of dashes, and free cholesterol, by a line of dots and dashes. At the foot of all the charts, the changes in the percentage of the serum cholesterol ester are shown. The high normal level is indicated by a line of dots and dashes.

Fig. 2.—Cholesterol changes in the serum of a representative rabbit (87) of the group 2*a* given, in addition to the regular diet, cholesterol in oil and potassium iodide.

Group 2 b (regular diet plus cholesterol, with potassium iodide added after six weeks).—The total serum cholesterol curve was similar to that of group 1 *a* for the first six weeks. At this time, when usually a drop set in, potassium iodide was added, and the cholesterol value remained stationary for that week instead of falling. After that the rise was very abrupt, going steadily upward, in some cases reaching a high level of 2,700 mg. per hundred cubic centimeters (low value, 1,422 mg.).

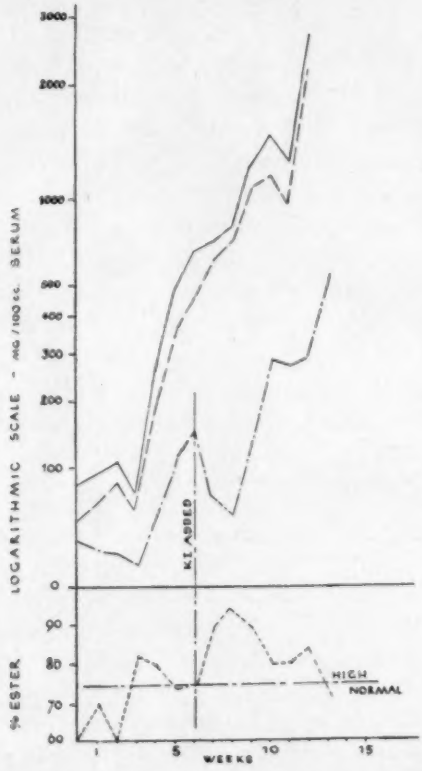

Fig. 3.—Cholesterol changes in the blood serum of a representative rabbit (26) in the group 3*b* given, in addition to the regular diet, cholesterol in oil to which six weeks later potassium iodide was added.

The relationship of cholesterol esters was definitely altered. Whereas for the period prior to the addition of potassium iodide cholesterol ester was 74 per cent, as found for all the rabbits to the diet of which cholesterol alone was added, after the administration of potassium iodide a sudden increase of the percentage occurred, reaching 90 and later 94. After six weeks, a gradual return to the high normal occurred. The average percentage of cholesterol ester after potassium iodide was added was 83 (fig. 3).

Group 3 a (regular diet plus cholesterol plus Jodtropon).—The findings for Jodtropon were similar to those for potassium iodide (group *2 a*), except that the rise of the total serum cholesterol was more abrupt with a steady incline and only an occasional divergence. The highest level reached was 2,662 mg. per hundred cubic centimeters.

The cholesterol ester relationship was similar to that when potassium iodide was administered, viz., 78 per cent (fig. 4).

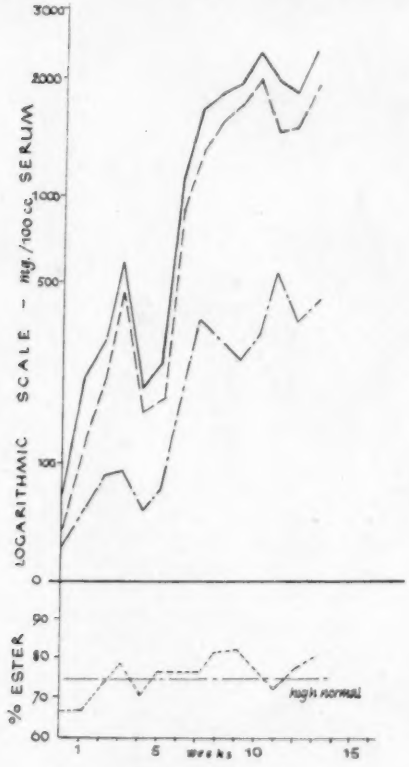

Figure 4

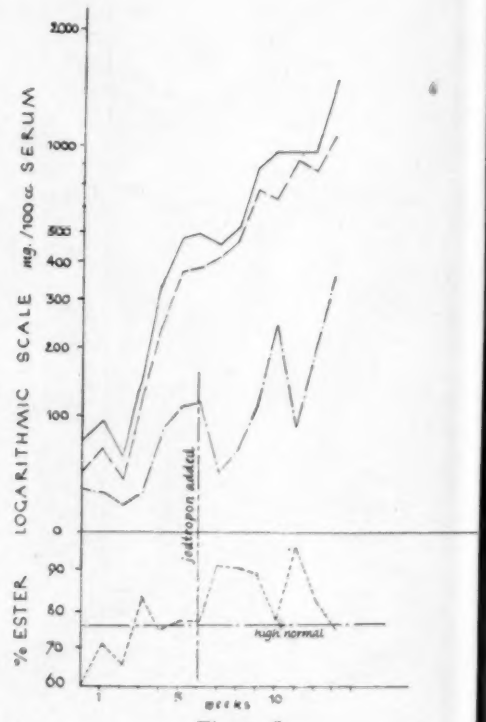

Figure 5

Fig. 4.—Cholesterol changes in the blood serum of a representative rabbit (*29*) in the group *3a* given, in addition to the regular diet, cholesterol in oil and Jodtropon.

Fig. 5.—Cholesterol changes in the blood serum of a representative rabbit (*27*) in the group *3b* given, in addition to the regular diet, cholesterol in oil to which Jodtropon was added six weeks later.

Group 3 b (regular diet plus cholesterol, with Jodtropon added after six weeks).—The blood cholesterol findings were similar to those for group *2 b*, except for a slight drop of the total cholesterol in the six weeks.

The cholesterol ester relationship was 74 per cent before and 83 per cent after the administration of Jodtropon (fig. 5).

Summary.—The serum cholesterol increased in all cases in which cholesterol in oil was fed. On the average, when cholesterol alone was added to the diet, the rise was slow in the first three weeks and then abrupt, reaching the high level of about 900 mg. per hundred cubic centimeters. When iodine in the form of potassium iodide or Jodtropon was fed along with cholesterol in oil, the rise in blood cholesterol was more acute and the levels reached were as high as 2,500 mg. per hundred cubic centimeters. If cholesterol in oil was first fed and then iodine added to the feeding, the course followed simulated the one taken when iodine was fed from the start, with similar high values. The sex of the animals made no appreciable difference to this relationship.

The cholesterol ester relationship reached high normal values (74 per cent) when cholesterol alone was added to the diet, and somewhat higher values when iodine was given simultaneously (78 per cent), but when cholesterol was fed and iodine added later, this relationship reached the high value of 94 per cent, with the average being 83 per cent. The cholesterol ester content of the blood remained high for six weeks, at which time it returned to normal.

In view of the possibility of an error of 5 per cent in the chemical technic employed, it may be conceded that the difference in percentage of cholesterol ester between the first two groups might become insignificant, but in the last group the difference is beyond the possibility of error.

AORTIC CHANGES

Group 1 a (cholesterol in oil added to diet).—There was a slight to moderate development of yellowish-gray, elevated plaques situated mostly about the mouths of the innominate, left subclavian, carotid and intercostal arteries.

The microscopic changes consisted of a subendothelial deposit of cholesterol ester, free and in histiocytes. There was a moderate amount of fat between the elastic fibers of the inner third of the media. This deposit was found as a rule along the distal aspects of the fibers. There was no elastic tissue proliferation but rather a spreading apart of the fibers.

Groups 2 a and 3 a (cholesterol and iodine added to diet).—The degree of lipoid deposit was more marked than in group 1. In addition to the deposit about the mouths of the vessels, there were plaques and long linear deposits along the posterior wall, not related to the intercostal arteries. To a lesser extent small plaques were found in the abdominal portion.

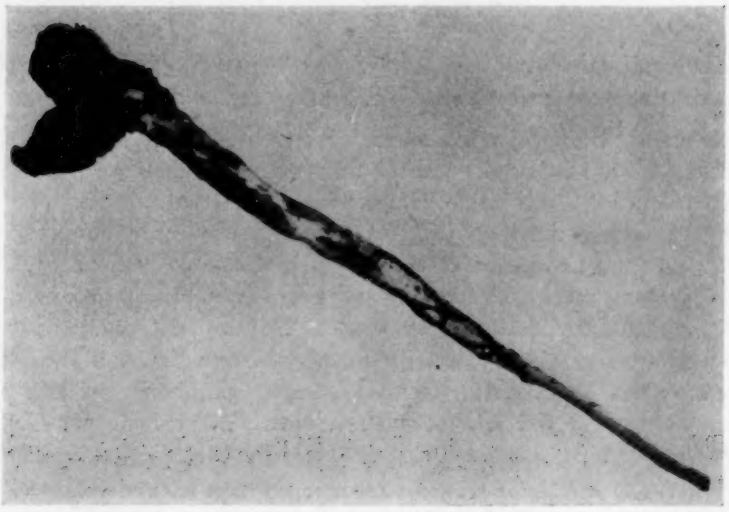

Fig. 6.—The aorta and heart of a rabbit fed, in addition to the regular diet, cholesterol in oil to which potassium iodide was added six weeks later (rabbit 26). The entire specimen was stained with sudan III. Note the marked lipoid deposit, especially in the thoracic portion (one half normal size).

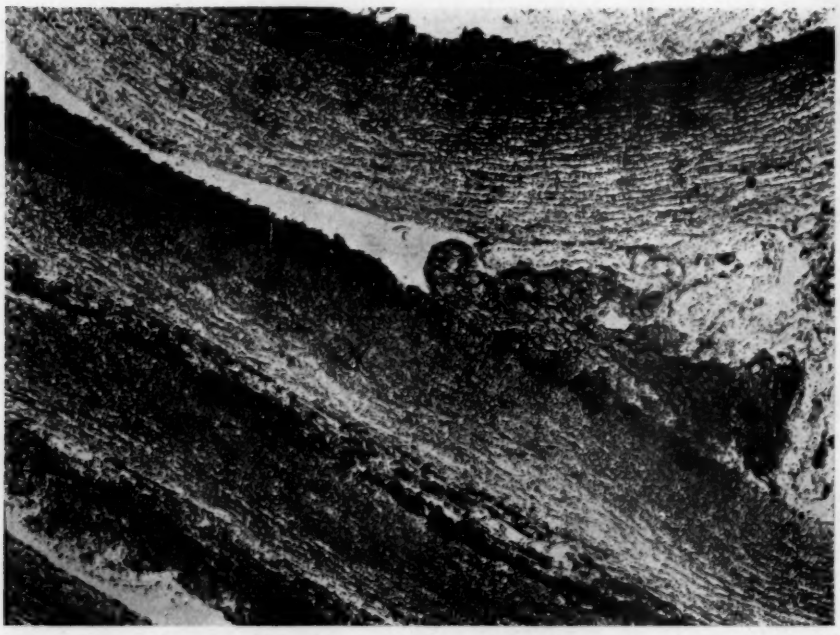

Fig. 7.—Several thicknesses of the aorta stained with sudan III. This rabbit was fed, in addition to the regular diet, cholesterol in oil to which after six weeks Jodtropon was added (rabbit 27). Note the marked lipoid deposit extending into the media (dark-staining substance); × 50.

The microscopic observations were similar to those in group 1 *a*, except that they were more pronounced. The intima became thickened by the lipoid deposit; there was a marked proliferation of histiocytes, and the elastic fibers of the inner media were spread far apart by the infiltrating lipoid. No elastic tissue proliferation was found.

Groups 2 b and 3 b (cholesterol added to the diet, with iodine preparations added after six weeks).—The aortas of this group showed the most marked changes. Figure 6 shows an aorta stained with sudan III in which practically the entire thoracic portion was infiltrated with fat, and to a lesser extent the abdominal portion.

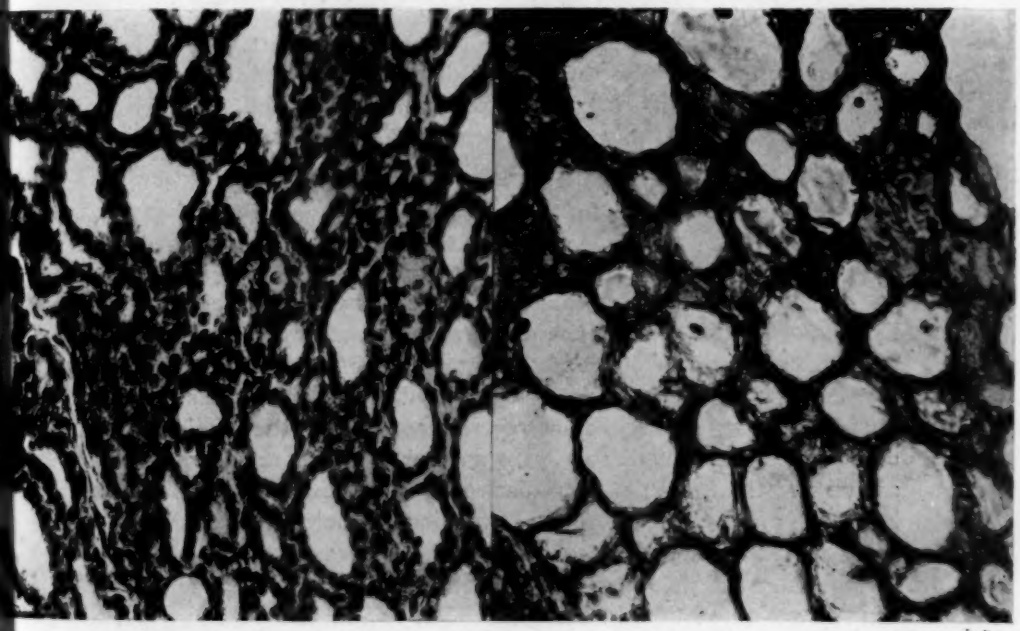

Fig. 8.—Left, thyroid gland of a rabbit which had cholesterol only added to its diet. Note the cuboidal epithelium and the small follicles. Right, thyroid gland of a rabbit which had both cholesterol and iodine added to its diet. Note the pavement epithelium and the large follicles (hematoxylin and eosin; × 500).

The microscopic changes are best seen in figure 7, which shows that the inner half of the aortic wall was infiltrated with fat. The intima was thickened either diffusely or in plaques by the infiltrating fat. No elastic tissue proliferation was found.

Summary.—In attempting to correlate the anatomic changes of the aorta with the blood findings it appeared that the amount of fat in the aorta was roughly proportional to the degree of hypercholesteremia, and that of the latter the ester was the important component (Aschoff, Anitschkow, Schönheimer).

CHANGES IN THE THYROID GLAND

In seeking to explain the action of the iodine, the thyroid glands were studied microscopically in all cases.[2] In group 1 the follicles were uniformly small, the epithelium from low cuboidal to cuboidal, and the colloid sparse in amount, staining rather pale pink with eosin (table; fig. 8, left). In groups 2 and 3 the follicles were larger than in group 1, the epithelium flat, and the colloid abundant, staining reddish pink with eosin. The glands were on the whole smaller than in group 1 (fig. 8, right).

The thyroid glands of group 1 (with or without cholesterol feeding) showed evidence of some activity, although the rabbits were killed at the beginning of the summer and had already been partaking of green food. In groups 2 and 3 there was a definite quiescence of the thyroid glands, unquestionably due to the administration of iodine (Webster, Irsigler). The absence of thyroid activity in the latter groups was also indicated by the weights of the animals; they gained from 150 to 500 Gm. (table).

CHOLESTEROL FINDINGS IN THE BILE AND IN THE LIVER

Whether or not the thyroid gland regulates the cholesterol metabolism is not known. Abelin showed in mice that after the administration of thyroxine the fat content of the organs was reduced before the basal metabolic rate was increased. He expressed the belief that this hormone is specific in regulating the fat requirement. If by the administration of iodine, as in groups 2 and 3, the amount of this hormone is reduced, a study of the excretion of cholesterol becomes important. The bile, being one of the mediums for the excretion of cholesterol (the intestine being the most important excretory organ), was examined. It must be borne in mind that possibilities of error may arise if the bile remains for any period of time in the gallbladder, as concentration may occur.

The normal cholesterol content of the rabbit's bile was found to be between 55 and 75 mg. per hundred cubic centimeters, mainly in the form of free cholesterol (Rothschild's normal values were from 40 to 50 mg. per hundred cubic centimeters). As not all the rabbits had sufficient bile for examination, only a limited number could be examined (table).

For group 1 the cholesterol content was 40 mg. per hundred cubic centimeters; for group 2 *b* (in the animal in which the highest blood cholesterol was found—2,770 mg. per hundred cubic centimeters—and in which the most marked aortic changes were noted) the cholesterol

2. The animals were killed within one or two weeks in the middle of June. They had already had grass added to their diet for about one month.

content of the bile was 15 mg. per hundred cubic centimeters; for group 3 *a* it varied from 91 to 157 mg.; for group 3 *b* it was 102 mg.

Rothschild found that after twenty-eight days of cholesterol feeding in rabbits the amount of cholesterol in the bile doubled (90 mg. per hundred cubic centimeters). After one hundred and fifty days it was trebled (160 mg.). The cholesterol in the blood was correspondingly increased, from 130 to 364 mg. per hundred cubic centimeters, respectively. Rothschild concluded that the bile cholesterol was proportionate to the blood cholesterol. This is not universally accepted.

Unfortunately the insufficient number of cases does not allow definite conclusions, and as Harley and Barratt have shown, the cholesterol excreted in the bile of herbivorous animals is for the most part resorbed. It is suggestive that in the cholesterol-fed rabbit the liver fails to accommodate quickly enough, and the excretion of cholesterol through the bile is insufficient. A further demonstration of this fact was seen in the determination of the cholesterol content of the liver (table).

Normally, the rabbit's liver contains from 0.11 to 0.13 Gm. of cholesterol (Wacker and Hueck found 0.13 Gm. to be normal). In the cholesterol-fed animals the liver contained from 0.25 to 0.63 Gm. of cholesterol (similar values were obtained by Wacker and Hueck, also Ellis and Gardner). When iodine was fed from the beginning, the amounts of total cholesterol varied from 0.82 to 1.58 Gm. When iodine was added later, the amounts were from 0.89 to 1.54 Gm.

The addition of iodine caused a marked retention of cholesterol not only in the blood but also in the liver. Whatever the action of the iodine was in the cases studied, the end-result seemed to be directed against the excretory parts of the liver.

There is yet to be explained the increase of cholesterol ester in the animals of groups 2 *b* and 3 *b* when the iodine was added later in the course of the cholesterol feeding.

Webster showed that when rabbits with large active thyroid glands are fed massive doses of iodine (7.5 Gm.) they lose a great deal of heat and rapidly die. When smaller doses of iodine are fed (1.5 Gm.) to animals with small active glands, the amount of heat produced is less and the animals survive. He interpreted this loss of heat as an indication of the amount of thyroxine liberated, the latter being proportional to the available iodine. Sections of the thyroid gland taken at frequent intervals during administration of iodine only showed a complete regression of these glands to the colloid type (Webster, Irsigler).

As has been described, the thyroid glands of the animals not fed iodine were slightly to moderately active. When iodine was administered to the cholesterol-fed animals, a regression of the glands probably took place with liberation of thyroxine, as shown by Webster. The increased secretion of this hormone was necessarily followed by an

Observations in Representative Animals from Each Group

Rabbit	Sex	Type of Feeding	Weight at Start, Gm.	Weight at End, Gm.	Cholesterol in Serum, Mg. per 100 Cc.						Aver. Percentage of Ester	Cholesterol in Bile, Mg. per 100 Cc.	Total Cholesterol in Liver, Gm.	Changes in Thyroid Gland	Changes in Aorta	Comment
					At Start		At End		Highest							
					Free	Ester	Free	Ester	Free	Ester						
A	M	Regular diet only	1,850	.....	27	48	...	.....	.....	.....	64	55	0.11	Low cuboidal epithelium, little colloid	None	No doubly refractive bodies in organs
B	M	Regular diet only	1,850	.....	22	56	...	.....	.....	.....	72	70	0.13	Low cuboidal epithelium, little colloid	None	No doubly refractive bodies in organs
83	F	Regular diet + cholesterol in oil	2,200	2,650	23	43.6	96	390	144.4	654.6	74	40	0.63	Low cuboidal epithelium, little colloid, follicles small	Slight amount of fat deposited in thoracic portion and about issuing vessels	Slight arcus lipoides, few doubly refractive bodies in aorta, liver, suprarenal glands
87	F	Regular diet + cholesterol + potassium iodide	1,950	2,400	30	45	458	2,027	366	2,081	79	..	1.58	Epithelium flat, much colloid in large follicles	Moderate to marked amount of fat in thoracic portion and slight deposit in abdominal portion	Slight arcus lipoides, numerous doubly retractive bodies in all organs
29	F	Regular diet + cholesterol + Jodtropon	2,075	2,150	11.4	24.85	590	2,070	590	2,070	77	157	0.8	Same as above	Same as above	Moderate arcus lipoides, numerous doubly refractive bodies in all organs
26	M	Regular diet + cholesterol, then potassium iodide added	2,350	2,850	34	40	568	2,202	568	2,202	Before iodine 74 After iodine 83	15	1.54	Same as above	Most marked diffuse deposit in thoracic, and to less extent, in abdominal, portion	Moderate arcus lipoides, numerous doubly refractive bodies in all organs
27	F	Regular diet + cholesterol, then Jodtropon added	2,130	2,600	29	42	358	1,064	358	1,064	Before iodine 74 After iodine 84	102	0.89	Same as above	Same as above	Same as above

increased metabolism which also influenced the liver. As the latter excretes only free cholesterol through the bile (Bürger, Thannhauser), there was a corresponding proportional increase of cholesterol ester in the blood. (The foregoing mechanism is offered only as a suggestion in view of the fact that the entire cholesterol metabolism of the rabbit under these experimental conditions is greatly disturbed.)

After a time when the thyroid gland was inactivated by the iodine, the normal relationship of free cholesterol to cholesterol ester was reestablished. The decrease in the general metabolic activity resulting from the inactivity of the thyroid gland may account for the relatively decreased excretion of cholesterol and for its storage in the body.

Kohno, Kunde, Leupold, Macciota (cited by Bürger), Abelin, and Turner and Khayat have found a decrease in the cholesterol content of the blood after feeding thyroxine, and Rohrschneider and Artoni found an increase after thyroidectomy (without disturbing the parathyroids). Besuglow and Tutkewitsch, by feeding thyroxine to dogs, found that the bile secretion was diminished as well as its cholesterol content, while following thyroidectomy the bile secretion was increased as well as its cholesterol content.

COMMENT

The action of iodine in the prevention or the acceleration of deposits of lipoid in the rabbit's aorta as seen from experimental studies is not direct but through the thyroid gland (Turner and Khayat). This activity is probably dependent on increased liberation of the thyroid hormone (Webster).

The doses of iodine given to the animals in this study were large physiologic ones (cf. Webster and Irsigler). That they were not toxic was noted by the inactivity of the thyroid gland, by the absence of microscopic degenerative changes in the aorta or other organs and by the increase in body weight.

The doses of iodine given by Liebig (in the form of an iodized fatty acid ester and by Turner (in the form of potassium iodide) were from 150 to 322 mg. of iodine per day respectively for an animal weighing 2 Kg. If it is assumed that the average human being weighs about 70 Kg., this would mean a daily consumption of from 5 to 10 Gm. of iodine (from 7 to 13 Gm. of potassium iodide). As Liebig has shown, if the iodine is excluded from the rabbit's diet for a short period (two or three weeks), the protective action of the iodine is to a great extent lost. The results given by Seel and Creuzberg, who used small doses of iodine (2 mg. of potassium iodide), could not be substantiated by me.

Granted that the cholesterol content of human blood rarely reaches the heights obtained in the rabbit, the point that is driven at is that the action of iodine is not a direct one but through its activation of the thyroid gland, and that the large physiologic doses cause regression of a gland that may be slightly active, with a resulting increase of the lipoid deposit in the aorta. Massive doses of iodine given over a longer period may not only be toxic directly (Liebig, Pfeiffer) but may stimulate the thyroid gland to activity (Raab, Pfeiffer). Indeed, it is only by the latter method that the prevention of atherosclerosis in the rabbit is brought about. If large physiologic doses are administered, an increased rather than a decreased deposit may take place.

From a clinical standpoint, the cholesterol content of the blood is decreased in exophthalmic goiter (Epstein and Lande, Kohno, Bing and Heckscher, cited by Friedland). Hurxthal found that usually under 100 mg. of cholesterol per hundred cubic centimeters of blood indicated a very toxic state, while over 200 mg. indicated a state varying from mildly toxic to normal (in hyperthyroidism). On administering compound solution of iodine, the blood cholesterol rose as the toxicity decreased. In some instances an increase of the blood cholesterol was found, but then the phosphorus fraction was also increased, speaking for destruction of nerve tissue (Omelyanovich-Pavlenko).

Atherosclerosis in persons with hyperthyroidism is uncommon (also Aschoff). On the contrary, in athyreosis, myxedema and cretinism, in which the blood cholesterol is increased (Luden, Heckscher, cited by Friedland), the incidence of atherosclerosis is higher (Heine, Bourneville). Wegelin and also Hellwig state that a definite myxedematous state is not necessary but that a mild to moderate hypofunction of the thyroid gland will suffice.

SUMMARY AND CONCLUSIONS

Large physiologic doses of iodine in the form of inorganic potassium iodide or organic Jodtropon produced a marked increase of the cholesterol in the blood and liver and a corresponding decrease of the cholesterol in the bile in cholesterol-fed rabbits. The hypercholesteremia thus produced was far beyond that of rabbits which had had cholesterol alone added to their diet.

When iodine was added later in the course of cholesterol feeding, the cholesterol esters of the blood increased for six weeks. It is suggested that in the rabbits in which the cholesterol metabolism was so markedly disturbed the action of the iodine on a slightly active gland caused a regression of the gland and in doing so liberated an increased amount of the thyroid hormone. The latter stimulated the general metabolism as well as the liver. As the liver excretes only free cholesterol through the bile, there was a corresponding proportional

increase of the cholesterol esters of the blood. The aortas of the latter animals presented the most marked lipoid deposit, stressing the importance of the cholesterol esters in experimental atherosclerosis.

A comparison of the thyroid glands of the animals fed iodine with those of the animals not fed iodine revealed a resting state of the colloid in the former and a slightly active state in the latter.

As the action of iodine in the prevention of deposits of lipoid in the aorta of the cholesterol-fed rabbit is dependent on increased thyroid activity, its employment in man should be guarded.

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ARGENTAFFINOMAS OF THE GASTRO-INTESTINAL TRACT, BENIGN AND MALIGNANT

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Oberndorfer [1] described a peculiar type of tumor of the gastro-intestinal tract and called it "carcinoid" because of its resemblance to carcinoma in histology but not in behavior. Gosset and Masson [2] showed that tumors of this type contain cytoplasmic granules which reduce silver ammonium oxide. Their work further demonstrated that these granules are present in the Kultschitzky cells of the intestinal mucosa. These had been described by Kultschitzky [3] as specialized epithelial cells in the crypts of Lieberkühn. The cells have been shown to occur occasionally in the stomach and to become fairly numerous in the duodenum while in the jejunum and ileum they are moderately abundant. They are most frequent in the appendix, but they can be demonstrated in small numbers in the colon (Maximow and Bloom [4]). Their function is not known, though Masson [5] suggested the possibility of endocrine secretion. Masson [6] and others have stated that these tumors are closely related to nerve fibers. By the use of a trichrome stain, Masson [6a] followed the budding of the Kultschitzky cells from the crypts of Lieberkühn and their subsequent migration into the nerve sheath of the underlying hyperplastic nerves or neuromas. In this location, the Kultschitzky cells proliferate and form tumors. Because of the presence of the specific silver granules in the cytoplasm of these neoplastic cells, the term "argentaffinoma" seems more descriptive than "carcinoid."

The earlier writers regarded all these tumors as benign. However, isolated reports of metastasizing argentaffinomas have appeared in the literature, and recently the more frequent occurrence of malignancy in this type of tumor has been recognized. Raiford [7] described six malignant argentaffinomas and collected twenty-eight additional instances

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From the Department of Pathology of the Peter Bent Brigham Hospital.

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from the literature. The same series was discussed later by Lewis and Geschickter [8] with the addition of two more cases. Besides these Masson and Martin [9] described a case of malignant argentaffinoma of the stomach. Christopher [10] presented an additional case with the primary tumor in the ileum. The total number of malignant argentaffinomas recorded, then, is thirty-eight.

It seems that comparison of the benign and malignant argentaffinomas may provide useful data in relation to their type of growth. Is the complexity of the stroma maintained outside the primary growth? Are all the elements represented in all the metastatic nodules or does the representation vary? To what extent is the character of the stroma dependent on the adjacent tissue? It would seem that those elements which follow the tumor beyond its original site and are seen in the metastases must be stimulated by the tumor cells.

MATERIAL

The material available for this study consisted of thirty-one argentaffin tumors of the gastro-intestinal tract obtained from twenty-one patients during the past seven years at the Peter Bent Brigham Hospital. The cases are described briefly in the table. These tumors occurred among 10,668 specimens of all types, a total incidence of 0.2 per cent. One had produced remote metastases, one was locally invasive, two invaded the musculature without penetration of the serosa, while the remaining twenty-seven tumors were entirely benign. One tumor was located in the stomach and was found incidentally at autopsy. A single benign argentaffinoma was located in the jejunum. The ileum was the site of sixteen tumors. This group included a locally invasive specimen as well as a tumor producing metastases to the liver and mesentery. Thirteen were seen in the appendix, two of which invaded the musculature, while all the others were confined to the mucosa and submucosa. None of these showed extension beyond the appendical serosa. There were no instances of argentaffin tumors of the colon in this series.

The entire series was studied microscopically in routine sections. Three of the tumors were chosen as representative of the various stages in argentaffinomas. The ones selected were a rather large benign tumor of the stomach, a locally invasive argentaffinoma of the ileum and an obstructive tumor of the ileum with metastases to the mesentery and liver. Sections from these were stained by many methods.

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Data in Thirty-One Cases of Argentaffinoma of the Gastro-Intestinal Tract

Patient	Sex	Age	Symptoms, Etc.	Location	Metastases
A	F	66	Reported in full. Case 1.....	Stomach	None
B	M	59	Death following resection of sigmoid for adenocarcinoma; argentaffin tumor incidental finding at autopsy	Jejunum	None
C	F	66	Acute purpura with secondary anemia (cause undetermined); tumor incidental finding at autopsy	Ileum	None
D	F	71	Generalized arteriosclerosis; myocardial infarction; tumors incidental finding at autopsy	Ileum (9)	None
E	F	41	Rheumatic heart disease with aortic and mitral stenosis and insufficiency; tumor incidental finding at autopsy	Ileum	None
F	F	64	Death following cholecystectomy for empyema of gallbladder; acute suppurative pancreatitis; multiple abscesses of liver; tumor incidental finding	Ileum	None
G	M	36	Tuberculoma of brain; bilateral tuberculosis of suprarenals; tumor incidental finding	Ileum	None
H	M	57	Reported in full. Case 2.....	Ileum (3)	One locally invasive; two benign
I	M	64	Reported in full. Case 3.....	Ileum	Mesentery, liver
J	F	17	Acute abdominal pain of twelve hours' duration, starting about umbilicus; spasm and tenderness in right lower quadrant	Appendix	None
K	F	20	Irregular menses, backache, ventral suspension of uterus; appendectomy	Appendix	None
L	F	21	Vague pain and tenderness constantly in right lower abdominal quadrant for seven years; acute exacerbation without nausea during that period; examination showed slight tenderness in right lower quadrant, maximal at McBurney's point; appendectomy	Appendix	None
M	F	17	Intermittent attacks of pain in right lower abdominal quadrant for two years; appendectomy	Appendix	None
N	F	41	Recurrent attacks of nausea, vomiting and constipation for six weeks; progressive enlargement of abdomen; supravaginal hysterectomy for leiomyomas of the uterus; incidental appendectomy	Appendix	None
O	M	28	Epigastric pain for two years, relieved by food and alkalis; excision of pylorus and adjacent duodenum for multiple peptic ulcers; incidental appendectomy	Appendix	None
P	F	41	Dull pain in lower part of abdomen for six days with constipation; bilateral salpingectomy for acute and chronic salpingitis; incidental appendectomy	Appendix	None
Q	F	44	Pain in lower part of back and dragging sensation in lower part of abdomen; uterine fixation and repair of pelvic floor; incidental appendectomy	Appendix	None
R	F	15	Acute abdominal pain, nausea and vomiting for twenty hours; diarrhea; no muscle spasm; temperature 99 F.; pulse 100; respirations 20; appendectomy	Appendix	Invasion of muscularis; no extra-appendical extensions; well two years later
S	F	35	Recurrent attacks of pain in right lower abdominal quadrant, accompanied by nausea; appendectomy; no attacks after operation	Appendix	None
T	F	20	Pain in right lower abdominal quadrant for five days; temperature 100 F.; tenderness, without muscle spasm, in right lower quadrant; operation showed acute salpingitis and periappendicitis; appendectomy	Appendix	None
U	F	25	Repeated attacks of pain in right lower quadrant for several years; severe pain maximal at McBurney's point for three days; appendectomy	Appendix	Invasion of muscularis; no extra-appendical extensions

PREPARATION OF MATERIAL

Fixation.—Tissue fixed in solutions of formaldehyde or Kaiserling's fluid was available in each case. Zenker's fluid also was used in cases 1 and 2, while in case 1 material had been fixed also in Bouin's fluid.[10a] In order to make use of stains requiring fixation in Zenker's fluid in the blocks from case 3, they were carried through ammonia by Davidoff's [11] method, mordanted in Zenker's fluid, and embedded. Sections from other paraffin blocks were mordanted on the slide.

Staining Methods.—All stains were applied to each tumor. For general study and nuclear detail hematoxylin-eosin and eosin-methylene blue were used. The stains for the intercellular substances were Mallory's aniline blue-acid fuchsin-phosphomolybdic acid-orange G, Van Gieson's hematoxylin-trinitrophenol-acid fuchsin, and Mallory's phosphotungstic acid-hematoxylin stain. Weigert's resorcinol-fuchsin stain was used to demonstrate elastic fibers. This was followed by various nuclear stains, usually basic fuchsin. Masson's [6a] method for the argentaffin granules ("silvering the sections") was used in all instances. Reticulum was studied by the Cajal-Maresch technic, followed by Van Gieson's trinitrophenol-acid fuchsin staining. This silver method stained the argentaffin granules. An attempt was made to secure silver impregnation of the nerves by Foot's [12] modification of Roger's method for paraffin sections, since this was developed especially to demonstrate the finest nerve fibers. As in the methods used by Masson, no satisfactory impregnation of the nerves was secured. However, the argentaffin granules were stained very intensely, so that the cytoplasm of the cells was filled with reduced silver. This was an undesirable result from the standpoint of histologic study but was an advantage in securing low power photomicrographs (fig. 7). The intense reaction was considered to depend on the pretreatment with ammoniated alcohol followed by 40 per cent silver nitrate.

CASE 1: BENIGN ARGENTAFFIN TUMOR OF STOMACH

Clinical Data.—M. H., a white woman 66 years old, was admitted to the hospital in a stuporous condition. She was found to have rheumatic heart disease. She had an excellent appetite. The bowels were regular, but the stools were nearly always loose. No melena was noted at any time. Death followed an extensive facial erysipelas. Autopsy showed the cardiac lesion to be aortic stenosis. A benign argentaffin tumor of the stomach was an incidental finding.

Gross Description.—The only lesion with which this investigation was concerned was the tumor of the stomach. The stomach was small and contracted. Externally no puckering of the serosa or infiltration of the gastrohepatic omentum was seen. There were no metastases demonstrable in any organ. The serosa was smooth, pale gray and glistening in all parts. The stomach was opened by a single incision along the greater curvature. It contained a small amount of partially digested food. No ulceration of the mucosa was noted at any point. On the lesser curvature, 4 cm. below the cardiac orifice, there was a tumor measuring 13 mm. in diameter. It was located in the submucosa, for it was covered by a

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10a. The formula for Bouin's fluid (Masson's modification) is: 40 per cent formaldehyde, 10 parts; water, 30 parts; glacial acetic acid, 2 parts, and trinitrophenol to saturation.

11. Davidoff, L. M.: Am. J. Path. **4**:493, 1928.

12. Foot, N. C.: Am. J. Path. **8**:769, 1932.

thin uninterrupted layer of mucosa which was slightly tense about its edges, while it could be moved freely over the tunica muscularis. There was no contraction of the gastric wall about the tumor. Neither here nor elsewhere in the stomach was there any change in the thickness of the tunica muscularis. A single cross-section of the tumor was made in the median plane. It was covered by an uninterrupted, thin layer of mucosa which was fused partially with the tumor. The cut section was yellowish gray and was firm in consistency. It was not entirely homogeneous, occasional tiny gray areas being seen scattered through the yellow tissue. No areas of necrosis or of hemorrhage were found. The entire freedom of the muscularis from invasion or distortion by the tumor was striking. The serosa was entirely normal.

Microscopic Description.—The surface was covered at all points by a thin but intact layer of mucosa. The glands were normal in size and arrangement. Kultschitzky cells were found in small numbers near the bases of the glands while the parietal and chief cells were present in their usual proportions. Spreading out from the lower portion of the mucosa was a tumor. While its connection with the mucosa could be traced, the bulk of the nodule occupied the submucosa. It was entirely discrete though no definite capsule was seen about the tumor. The type cell was a small one with an oval nucleus and a scanty cytoplasm. The cytoplasm was filled with very numerous argentaffin granules. Each cell was demarcated clearly in most portions from those adjacent to it, and often in the stained section there were spaces between the cells without reticulum or other stromal fibers. In other areas the tumor cells were arranged compactly. There were no mitoses, and giant cells were not seen. The cells in all parts of the tumor were strikingly uniform in size and shape. The stroma divided the tumor cells into rather large masses. A few very delicate reticular fibers passed into the masses but at the centers these were not seen. The larger groups of stromal fibers were complex in structure. There were large numbers of smooth muscle fibers in compact groups while a few of these extended into the finer ramifications of the stroma. In close association with the muscle fibers there was an unusual degree of hyperplasia of the elastica. By study of comparable sections stained with Weigert's resorcinol-fuchsin and Mallory's aniline blue connective tissue stain, it was noticed that the areas in which smooth muscle fibers were most numerous were the locations in which the increase in elastica was greatest. Collagen fibers were present in moderate numbers. These were associated with an abundant reticular network which was confined mostly to the larger masses of stromal fibers, passing occasionally into the larger clumps of tumor cells. No nerve fibers could be impregnated by the Foot-Rogers[12] technic. A careful study of sections stained with Mallory's aniline blue connective tissue stain and Mallory's phosphotungstic acid-hematoxylin stain left some doubt as to the presence of nerve hyperplasia. At any rate it was not so prominent as the increase in elastica or in smooth muscle. On the whole, the tumor contained few blood vessels. These had a single layer of elastica for the internal elastic membrane. There was a definite hyperplasia of the elastica in the adventitia, the fibers extending for a short distance into the tumor as an integral part of the stroma. No areas of necrosis were found. The tunica muscularis was uniform in thickness beneath the tumor. There was no evidence of tumor invasion or distortion of this structure. The serosa showed no change.

CASE 2: ARGENTAFFIN TUMOR OF THE ILEUM WITH INVASION OF THE MESENTERY BUT WITHOUT REMOTE METASTASES; MULTIPLE BENIGN ARGENTAFFINOMAS

Clinical Data.—M. O., a white man 57 years of age, entered the hospital for treatment of a cerebral tumor. He had not had any symptoms which could be referred to lesions of the gastro-intestinal tract. A large frontal meningioma was removed. On the thirtieth day after operation the patient died of pulmonary embolism following thrombosis of the left iliac vein. The argentaffin tumors were incidental findings at autopsy.

Gross Description.—The lesion with which this investigation was concerned was an argentaffin tumor located 2 cm. above the ileocecal valve. A firm, grayish-white mass was found in this position along the mesenteric attachment. This extended about half way around the circumference of the ileum and protruded from the serosal surface as a slightly elevated, puckered nodule. The ileum proximal to the tumor mass was very slightly dilated while distally it was normal in diameter. The mesenteric fat was adherent to the tumor and on section was seen to contain firm tissue of fibrous consistency in large amounts. The dense connective tissue extended along the adjacent mesentery for 3 cm. At the limit of extension of the tumor into the mesentery there was a firm mass 0.3 cm. in diameter. It was demarcated clearly from the adjacent fat, which was puckered and contracted.

After fixation, the ileum was opened along the free margin. It could be seen then that the tumor arose from the mesenteric border of the intestine and projected into the lumen so as to narrow it but slightly. The diameter of the ileum was little larger above the tumor than below. The lymphoid tissue of Peyer's patches was not altered. The nodule of tumor itself was 10 mm. in greatest longitudinal diameter and 5 mm. in elevation above the surrounding ileal mucosa. The mucosa was intact in all parts. A cut section showed tissue of firm, resilient consistency. No ulcerations of the thin mucosa could be found. The submucosa was widened, but the bulk of the nodule was composed of the hypertrophied and distorted tunica muscularis. The circular layer was very thick, and in a longitudinal section its fasciculi radiated from a puckered, densely fibrous center, being separated from each other by delicate cords of tumor. The neoplasm here as in the mesentery presented a pale yellow, firm surface without any evidence of hemorrhage or necrosis.

Two benign argentaffin tumors were found in the ileum of this subject. One, 4 mm. in diameter, was located 2 meters, and another, 2 mm. in diameter, was seen 1.5 meters, from the ileocecal valve.

Microscopic Description.—Over the surface of the tumor there was a thin layer of mucosa. Masses of tumor cells could be seen throughout the mucosa but most often in close relation to the bases of the glands. However, most of the neoplasm was situated in the submucosa with extension into the muscularis and through it to the mesentery. The type cell was a small one with an oval nucleus and scanty granular cytoplasm. Such cells tended to grow in masses, which varied considerably in size. There was very little evidence of cell membrane, the cytoplasm of adjacent cells blending closely. It contained many argentaffin granules. Mitoses were not found after careful examination. There were no tumor giant cells. The type of cell making up the tumor was remarkably uniform in all portions. The stroma of the neoplasm was composed of various elements. Smooth muscle was abundant. This was derived in part from the hypertrophied muscularis

mucosae, but it extended into the smaller ramifications of the stroma, in which place its derivation could not be traced with certainty. Elastic tissue was present as an integral part of the stroma, being most abundant in those locations in which there were groups of smooth muscle fibers, but extending freely into other portions. Collagen fibers were seen in moderate numbers and were associated with a delicate reticulum. There was a moderate degree of hypertrophy of the circular layer of the tunica muscularis. This was invaded by small groups of argentaffin cells with but little destruction of the muscle fasciculi. The tumor tended to grow in the deeper layers beyond the muscularis. In this outer portion, the stroma was composed almost entirely of very dense collagenous tissue. The distortion produced by this part of the tumor was considered the cause for the buckling of the circular layer of muscle. The extensions into the mesentery were similar to the portions of the tumor already described. No demarcation could be made out in the sections between them and the intra-intestinal growth. In the blood vessels no changes in the intima were noted. There was a slight hypertrophy of the elastica in the adventitia. No neoplastic cells were seen within endothelial-lined spaces.

Sections through the mesentery parallel with the long axis of the intestine showed cords of tumor invading the fat. The stroma was made up of very dense collagenous tissue, accounting for the puckering of the fat which was noted grossly. In the tumor were several nerves. Some of them were invaded by the tumor. Elastic tissue fibers were even more numerous than in the primary tumor. Sections of numerous mesenteric lymph nodes showed no metastatic neoplasm. No tumor cells were seen within lymphatics.

CASE 3: MALIGNANT ARGENTAFFIN TUMOR OF THE ILEUM WITH METASTASES TO THE MESENTERY AND LIVER

Clinical Data.—C. S., a white man 64 years old, entered the hospital complaining of severe constipation, which he had had six weeks. He had been entirely well until two years before admission, at which time he had an attack of constipation associated with nausea and vomiting. This subsided without medical attention after five days. During the intervening two years he had several similar attacks, the last of which occurred six weeks previously. After that, there were intermittent nausea and vomiting, which were accompanied by mild abdominal distention and cramplike pain in the epigastrium and about the umbilicus. The patient lost 17 pounds (7.7 Kg.) in weight during the six weeks. No definite history of melena could be obtained. Physical examination showed an emaciated elderly man in acute pain. The abdomen was slightly distended. Synchronous with the attacks of pain a mass that was tender could be palpated in the left lower quadrant of the abdomen. Between paroxysms of pain, the abdomen was free from masses. On the day following admission a large segment of ileum and its mesentery was resected. Ileocecostomy was performed. The ileum contained a constricting tumor, and there were masses of neoplastic tissue in the mesentery. At that time, tumor nodules could be palpated in the liver. None of these was removed. After operation, the patient did well. He was no longer troubled by distention of the abdomen, and he could have normal bowel movements. He was discharged from the hospital on the thirty-first day after operation. When seen six months later the patient was symptom-free.

Gross Description.—The specimen consisted of a portion of the distal ileum measuring 148 cm. in length. About the midpoint of the specimen there was a

constriction roughly dividing it into two equal parts. The constriction was formed by a tumor, which was seen as a firm spherical mass measuring 15 by 15 mm. in its greatest dimensions (fig. 2). A triangular portion of mesentery was attached, which measured 80 mm. in length. At its apex was a mass of tissue which was composed not only of what appeared to be lymph nodes but also of a considerable amount of cicatrized fat tissue into which some tumor had infiltrated. The nodes were gathered in a cluster and together with the regional fat formed a mass which measured 4 by 4 by 3 cm. On section this large firm mass presented along its distal half a fairly well demarcated group of nodules which seemed to be encap-

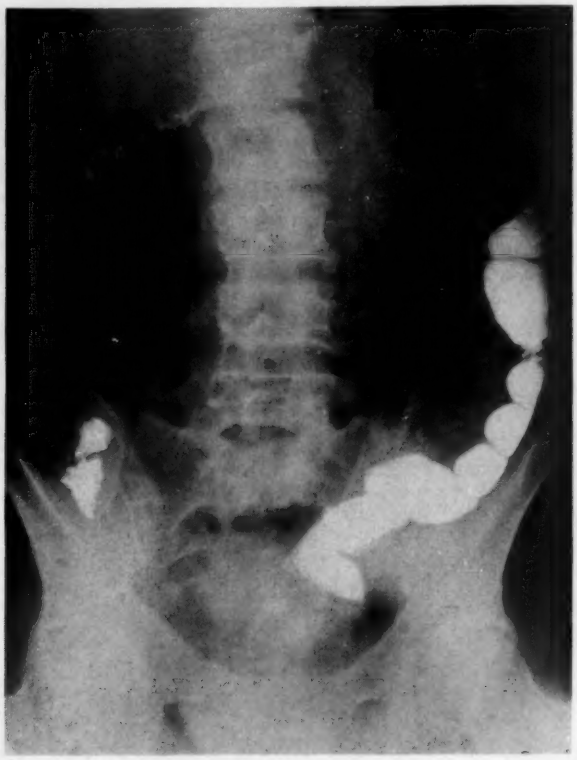

Fig. 1 (case 3).—Complete obstruction of the small intestine caused by a malignant argentaffinoma. The colon contains barium. Note the enormous distention of the loops of small intestine which the slowly progressive nature of the obstructing lesion permits. This type of roentgenogram has been seen in several cases reported in the literature.

sulated by the fibrous tissue. The peculiar lemon yellow color of the neoplasm was striking. These nodules were uniform in texture and number except in occasional areas where there was a brownish-black pigmentation. Along the distal margin of the nodules there was a definite zone of dense connective tissue which demarcated the firm yellow neoplasm from the regional fat comprising the remainder of the tumor in the mesentery. The bowel mucosa throughout its extent was intact. The Peyer's patches, which were few in number, were small and showed

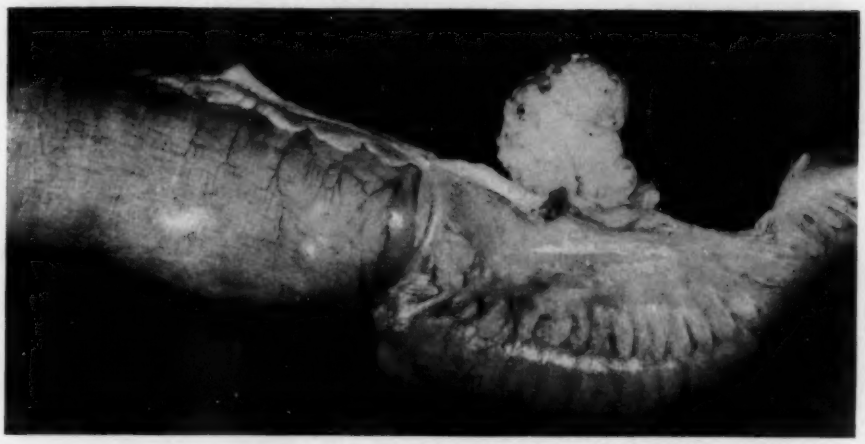

Fig. 2 (case 3).—Photograph of the gross surgical specimen. The lesion appears annular, but the intestine pouches out unevenly above the constriction.

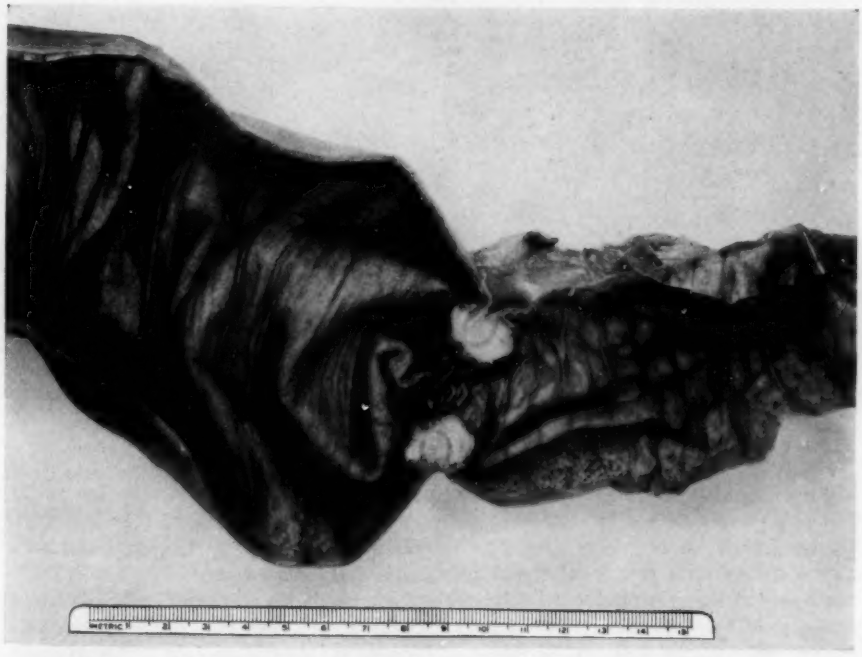

Fig. 3 (case 3).—The intestine has been opened. The lesion encircles only a part of the circumference. Note the dilatation of the intestine above the lesion. No ulceration is evident.

no lesions. Proximal to the constricting lesion the villous folds which encircled the lumen of the bowel were quite prominent, averaging 3 mm. in height a short distance above the obstruction. There was also some hypertrophy of the muscularis, so that this layer measured 1 mm. in thickness. At a distance of 6 cm. above the obstructing lesion the villous folds became somewhat flattened out and lost their prominence. At this point the ileum was 14 cm. in circumference. At the point of obstruction it was 2 cm. in circumference. This narrowing of the lumen was due largely to the presence of a constricting tumor which was situated opposite the attachment of the mesentery. The lumen was approximately 2 mm.

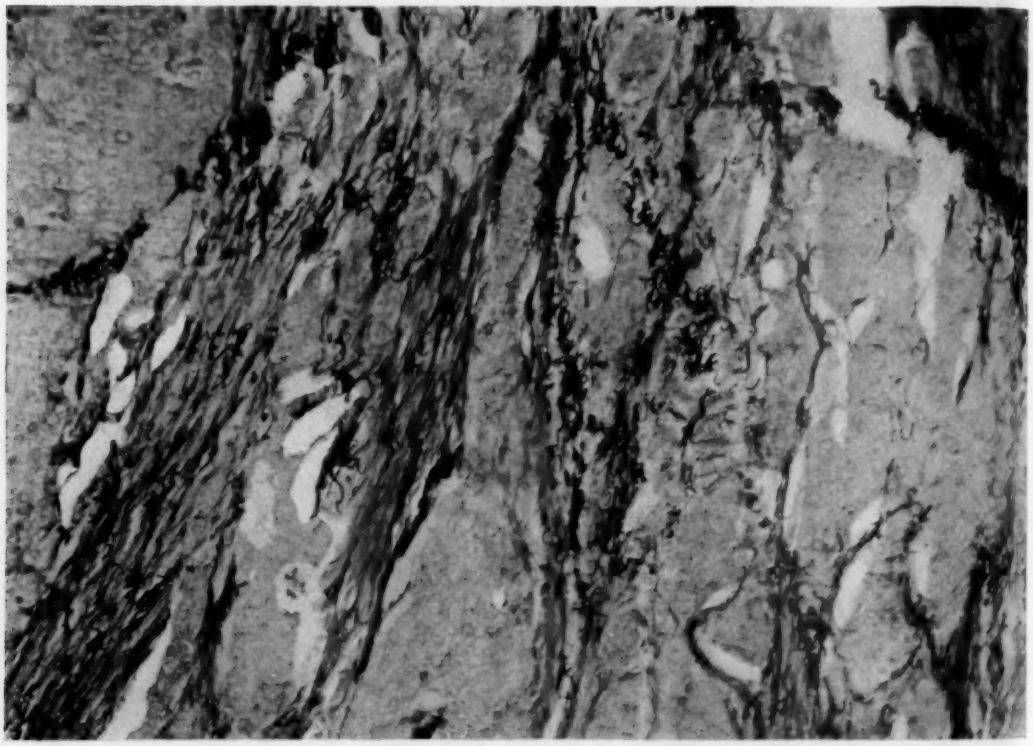

Fig. 4 (case 3).—Weigert's resorcinol-fuchsin stain counterstained with eosin; × 210. This shows the abundance of elastica in the primary tumor.

in diameter but was partially closed by the folds of mucosa so that a probe could be passed only with difficulty. The tumor nodule involved no more than half the circumference of the ileum (fig. 3). It measured 18 by 12 by 12 mm. Beneath the mucosal surface and the tunica muscularis there was a zone of tumor which averaged 4 mm. in thickness. The tunica muscularis was drawn sharply in and angulated, forming a horseshoe-shaped coat of muscle with the convexity toward the lumen and the open end of the angulation at the serosal surface. The muscularis seemed to be interrupted in a few areas by tumor, but there was extension of the tumor through the tunica muscularis so as to replace and to invade the serosa. The fatty tissue was puckered at the mesentery as if invaded by neoplasm.

Microscopic Description.—Blocks from the primary tumor and its mesenteric metastases were studied. In addition, serial blocks of mesentery from the primary tumor to the metastases were examined.

The primary tumor had the characteristic structure of an argentaffinoma. At each margin of the tumor there was ileal mucosa of average thickness. Its glands were uniform and contained only the usual number of argentaffin cells, these seldom exceeding three to a gland. The muscularis mucosae was normal. No hyperplasia

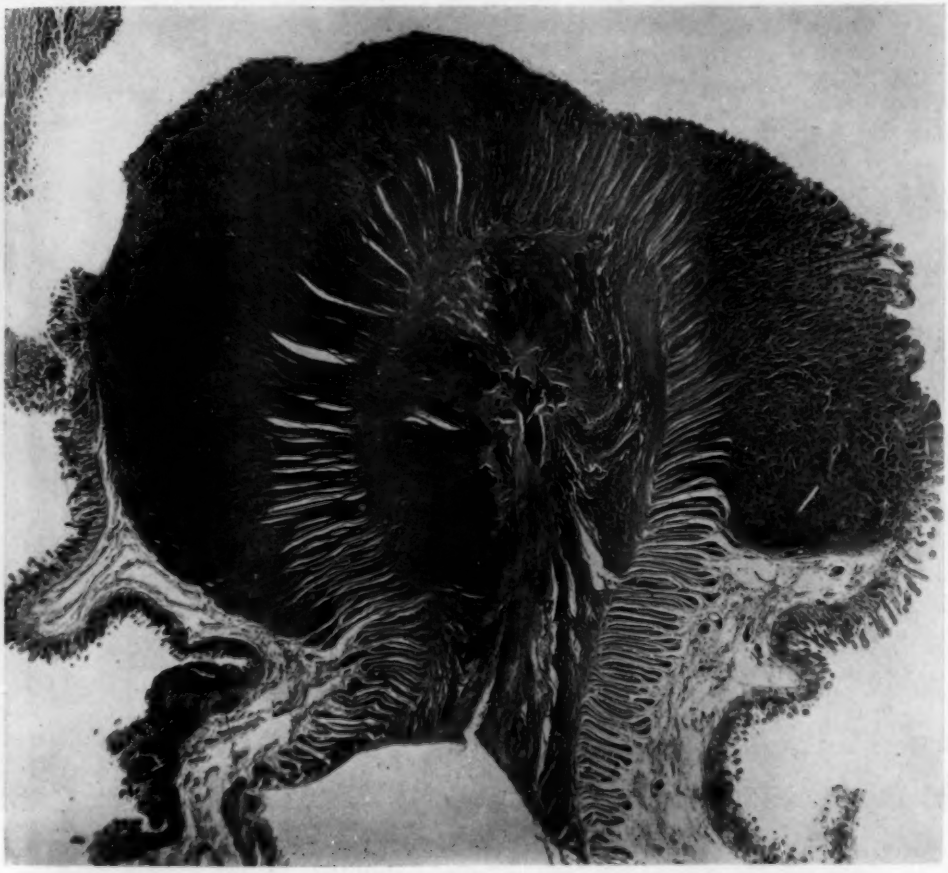

Fig. 5 (case 3).—Photomicrograph showing the growth of the tumor in the extramuscular layers with buckling of the tunica muscularis; × 9.

of smooth muscle, nerves or elastic tissue was noted. In the center of the tumor it was seen that the overlying mucosa was preserved very completely. From the bases of the deeper glands small groups of tumor cells extended downward into the submucosa. These were more or less independent of each other. They soon coalesced and in the submucosa formed a mass of neoplastic tissue. Here the cells were arranged in large masses into which a few reticular and elastic tissue fibers penetrated. The individual cells were small with oval nuclei, which contained delicately arranged chromatin material and which usually showed a single

nucleolus, staining especially well with the metachromatic silver technics. The cytoplasm occupied a relatively small proportion of the total cell volume. At the edges of the cell masses and in the actively advancing part of the tumor the cytoplasm was filled with fine argentaffin granules indistinguishable from those of the Kultschitzky cells of the intestine. The centers of the cell masses did not preserve these granules so well, though a few could be found in most cases. No mitoses were seen in any of the tumor cells. An alveolar arrangement was recognized frequently in which a row of cells surrounded a small lumen. The nuclei were adjacent to the lumen, the argentaffin granules being at the base of the cell just

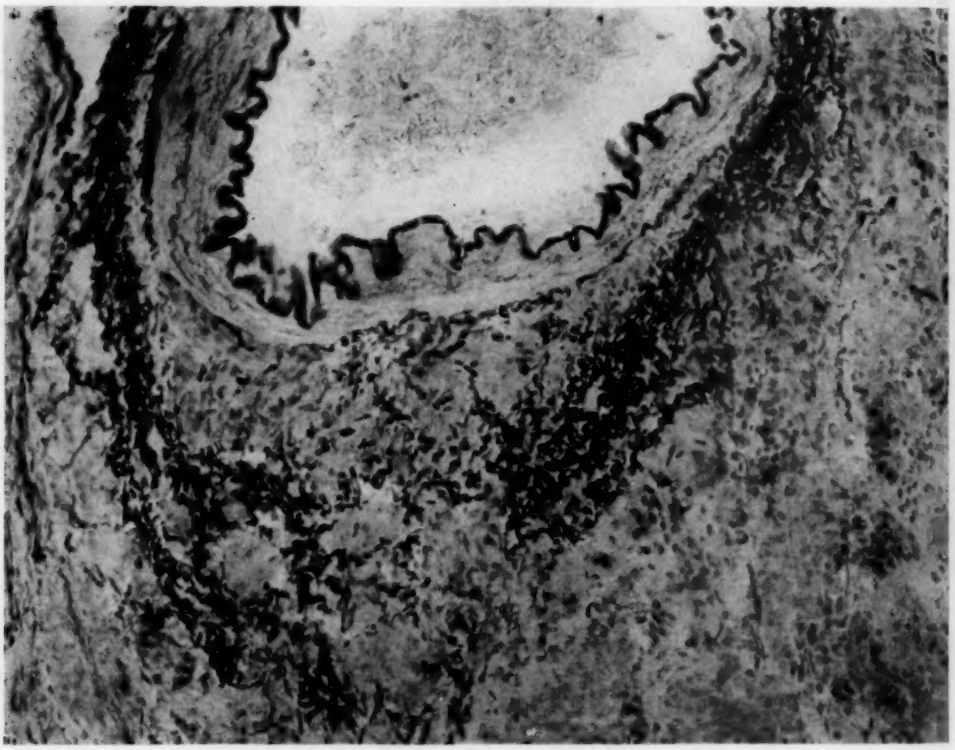

Fig. 6 (case 3).—Weigert's resorcinol-fuchsin stain lightly counterstained with basic fuchsin; × 210. This shows the proliferation of elastic fibers in the adventitia of a blood vessel in the mesentery with extension of these fibers into the tumor.

as in normal Kultschitzky cells. There were instances of reduplication in layers so as to form the masses of indistinctly demarcated cells farther from the lumen.

At the center, the muscularis mucosae blended with the stroma but could be recognized at the edges even within the confines of the tumor. The stroma was of great complexity and appeared to be derived from the muscularis mucosae, the submucosa and the tunica muscularis. In this tumor specific staining technics showed that all the elements of the submucosa, as well as of the muscular layers above and below it, participated in the formation of the stroma of the argentaffinoma, and not the neuromuscular complex alone. There was judged to be a slight

hyperplasia of nerve fibers, which could not be impregnated by the Foot-Rogers technic. The smooth muscle was more abundant and passed throughout the dense cord of tissue which separated the neoplastic masses. A delicate argyrophilic reticulum was found in all parts of the tumor stroma. Of special interest was the increase in elastic tissue fibers. These at times formed dense limiting membranes about cell masses and at others were matted together with the smooth muscle or extended as single strands along the stroma. In the thick bands of connective tissue which separated the groups of tumor cells, collagenous fibers were abundant.

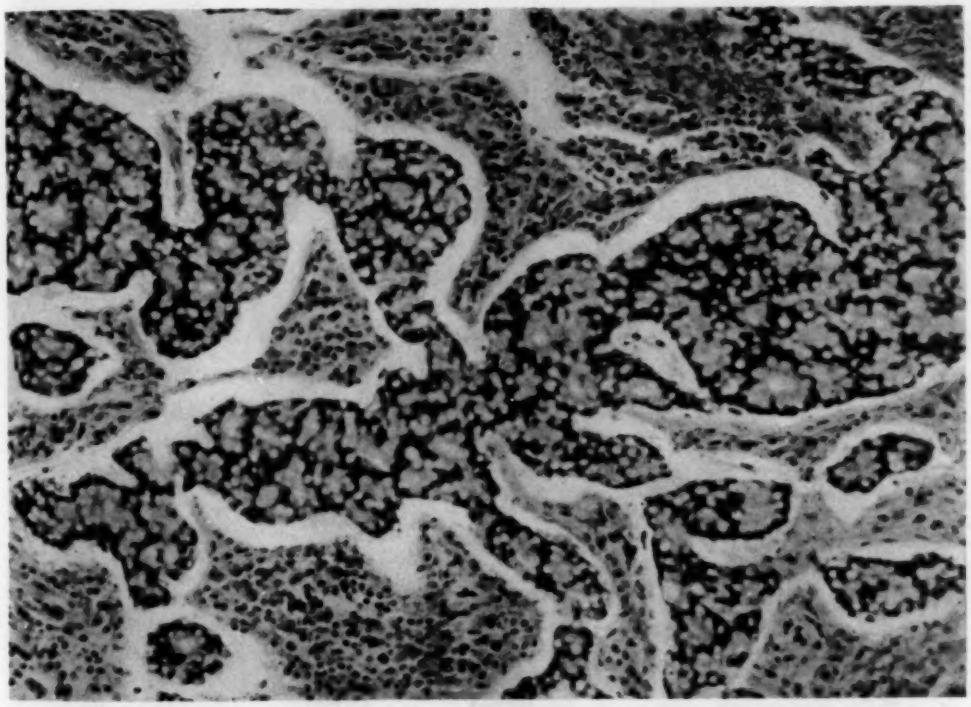

Fig. 7 (case 3).—Mesenteric metastasis; Foot-Rogers method; × 325. This shows small groups of cells invading a lymph node. The argentaffin granules are intense black. No nerves are impregnated. The alveolar arrangement is more pronounced here than in most parts of the tumor.

Only a small portion of the constricting tumor was found in the submucosa. The muscularis was hypertrophied enormously about a central core made up of tumor with a dense fibrous stroma which caused scarring and distortion, so that a section taken longitudinally showed the muscle fasciculi spread out like the ribs of a fan (fig. 5). Small groups of argentaffin tumor cells were seen scattered through the tunica muscularis. Coarse elastic tissue fibers accompanied the fasciculi, and a dense group of fibers of this type followed the outer border of the circular layer somewhat like a limiting membrane. Beyond this point, larger groups of tumor cells were found, and the same complex stroma intervened. On

the whole, the neoplasm was not very vascular, and no tumor cells were seen within endothelial-lined spaces.

The tissue between the primary growth and the metastasis was examined by serial blocks 3 mm. thick. Strands of tumor cells followed blood vessels freely through the fat. These blood vessels showed a marked hyperplasia of the elastic tissue of the adventitia with extension of these fibers into the tumor as though the tumor were stimulating the formation of elastic tissue fibers for its stroma from this source. The intima was thickened, and reduplication of the internal

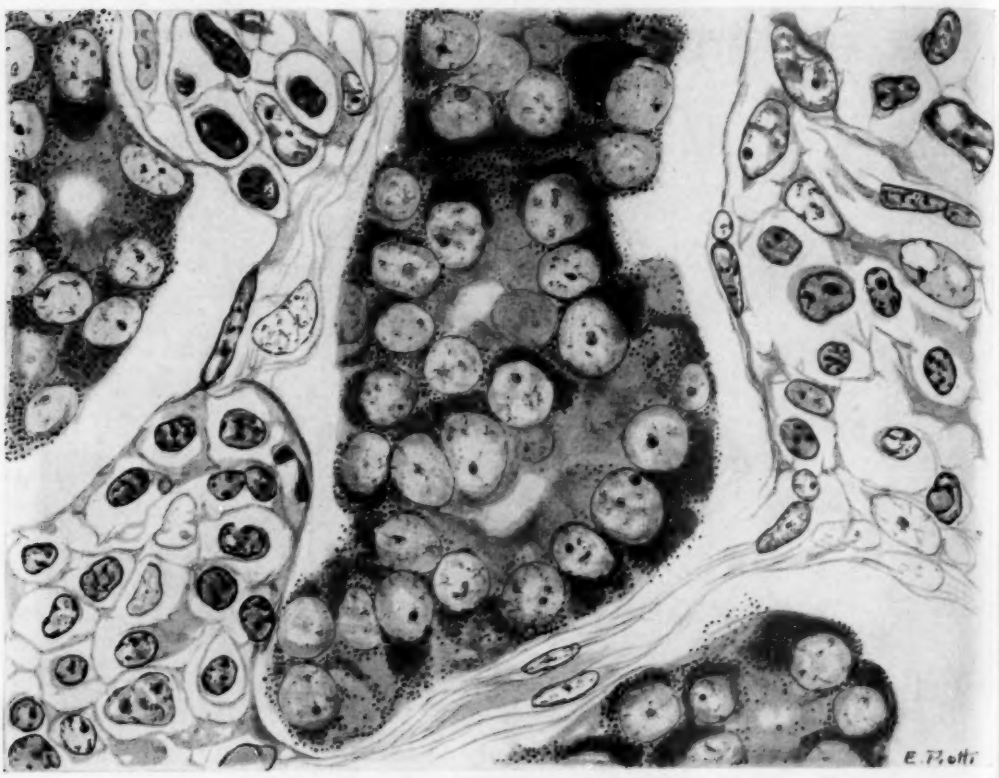

Fig. 8 (case 3).—Camera lucida drawing, × 1,300, showing a portion of a mesenteric lymph node infiltrated by metastatic argentaffinoma. The staining is by Masson's method for "silvering the sections," counterstained with alkaline methylene blue. In the center and at each side of the drawing there are clusters of tumor cells separated from each other by lymphoid tissue. The cytoplasm of each tumor cell is filled with specific argentaffin granules.

elastic membrane was seen in some vessels. There was also some hypertrophy of the smooth muscle of the media. No tumor cells were seen within lymphatics.

The metastastis was situated, not in lymph nodes primarily, but just outside. The nodes were invaded by small groups of actively growing tumor cells. The metastasis was composed chiefly of groups of argentaffin cells with cytoplasms poorly demarcated from one another. Among these groups very little reticulum

or other stromal fibers extended. The smaller groups showed a greater tendency to alveolar formation. The argentaffin granules stained very intensely. The stroma was made up of very dense bands of collagenous tissue in which smooth muscle was identified in small amounts. Thin, delicate elastic tissue fibers were seen especially in the dense outer covering of the tumor. They closely paralleled the distribution of smooth muscle. No association of nerves with the stroma of the mesenteric cords or with that of the metastasis was apparent.

Unfortunately, no material from the metastasis in the liver was secured. The presence of a malignant tumor of the small intestine in connection with nodules of tumor in the liver would be presumptive evidence of their identity.

COMMENT

A series of thirty-one argentaffin tumors of the gastro-intestinal tract has been presented with a detailed description of three of them. Each of the three is considered representative of a different type in relation to malignancy. The large tumor of the stomach was entirely benign and has been chosen to represent this group because the total volume of argentaffin tissue was approximately the same as that of the intra-intestinal portion of the other tumors. The second case was one of local invasion; the third, of definite malignancy with production of distant metastases.

Each of these tumors consists of two parts, and each part has its special interest. The argentaffin cells are clearly the neoplastic ones. Their origin from the Kultschitzky cells of the intestine cannot be questioned. However, the germ layer from which the Kultschitzky cells are derived is by no means certain. Masson [6b] and Maximow and Bloom [4] stated that they are entodermal in origin. This is suggested by their intimate connection with the entodermal cells of the mucosal glands, in which location they can be recognized by the characteristic silver reduction of their granules as early as the fourth month of fetal life, much sooner than the granules of the cells of Paneth can be identified. Schack [13] confirmed this view. He stated that in the embryo the argentaffin cells appear first in the mucosal glands and that their presence elsewhere is the result of subsequent migration. Kull,[14] however, expressed the belief that the Kultschitzky cells arise from the mesoderm and migrate early in fetal life to lie in their close association with the entodermal elements of the mucosa. Raiford,[7] on the other hand, considered that an ectodermal origin could be postulated because of the association with nerves as described by Masson and because argyrophilic properties are a common characteristic of ectodermal cells while those of the entoderm do not show such an affinity. However, the silver impregnation of many mesodermal structures is recognized widely. Entodermal cells frequently contain the Golgi apparatus, which can be

13. Schack, L.: Beitr. z. path. Anat. u. z. allg. Path. **90**:441, 1932-1933.

14. Kull, H.: Ztschr. f. mikro-anat. Forsch. **2**:163, 1925.

demonstrated by silver impregnation. In later communications Masson [6] reiterated his belief that these cells are of entodermal origin. If argentaffinomas are inseparable from nerves, the nerves concerned are entodermal too, in his opinion.

The stroma of argentaffinomas is remarkable for its complexity. The presence of a hyperplasia of the nerves has been emphasized by Masson.[6a] He considered the tumor to begin as a neuroma, with subsequent migration of the argentaffin cells into the nerve sheath. In this location these cells undergo neoplasia. However, other writers have been unable to demonstrate a constant hyperplasia of the nerves, and the migration within the nerve sheath has not been seen by several investigators, including Raiford,[7] who looked with special care for it. Hyperplasia of the nerves has not been demonstrated beyond the intestinal serosa by any observer. Case 2 in this series showed invasion of nerve trunks in the mesentery.

Like all epithelial tumors argentaffinomas present in their stroma a variable number of collagenous fibers. These fibers vary in number, but more particularly in collagen production, in different locations. In the tumors studied the stroma contained a moderate number of such fibers in the mucosa, submucosa and tunica muscularis. However, in the masses of tumor in cases 2 and 3 which formed at the serosa there was very extensive collagen formation. This same dense collagenous tissue surrounded the mesenteric metastasis in case 3, while the cords of tumor extending between the primary growths and this point were accompanied by very delicate fibers of this type. In all tumors of this type argyrophilic reticular fibers are numerous, especially in association with the less dense collagen. While the reticulum extends into the masses of tumor cells farther than the other fibers, there are masses of argentaffin cells into which no stromal element can be seen to penetrate.

The presence of smooth muscle fibers in the stroma of the intraintestinal section has been recognized by many observers. These fibers appear to be derived in part from the muscularis mucosae and in part from the tunica muscularis. The formation of smooth muscle is stimulated at the sites in which it is normally present. In the present material one could never be sure of its derivation from the media of blood vessels. Furthermore, smooth muscle as a stromal element has not been found in the mesenteric extension or in the mesenteric metastasis of the malignant ones. It occurs in groups, occasionally ending in isolated muscle cells in the smaller stromal masses.

No special studies have been found in the literature on the elastic tissue element in argentaffinomas. Accordingly, these fibers have been studied in detail in all locations. Elastica is found to be very abundant in both benign and malignant tumors of this type. At times the fibers are found in clusters and at others they are scattered through the

collagenous tissue passing into the finer radices of the stroma. Usually it is associated in location with smooth muscle. When large masses of elastica are found, comparable sections stained with Mallory's aniline blue connective tissue stain demonstrate smooth muscle in the same location. This is an association pointed out in the case of nerve fibers. In case 3 the elastica was found in the stroma of the tumor cords in the mesentery and in that of the metastasis. It thus does not show the restriction to the intra-intestinal portions of argentaffinomas seen with smooth muscle and nerve fibers. In several places, but most clearly in case 1 and in the cords of tumor in the mesentery in case 3, the origin of the elastic tissue fibers from the adventitia of small and medium-sized blood vessels has been demonstrated. In such areas, there is a hyperplasia of the elastica in the adventitia with extension of the fibers among the masses of tumor cells, the number of fibers becoming progressively less the greater the distance from the vessel (fig. 6). Whether all the elastic tissue has such an origin cannot be stated with certainty. It is considered more probable that much of that seen in the intra-intestinal tumors is derived from the elastica normally present in the submucosa. Thus, these tumors are shown to have the property, apparently rare among tumors, of stimulating the production of elastic tissue fibers. In exceptional cases of many types of tumor elastic fibers are found in abundance. These are largely, if not wholly, the elastica of the tissue invaded by the neoplasm. They are not stimulated by the desmoplastic properties of the tumor. Such findings are not constant for any particular type of neoplasm. In all the instances of argentaffinoma studied, an abundance of elastic tissue fibers has been seen. The proliferation of the elastica of the adventitia of blood vessels is a striking feature and illustrates the ability of these tumors to stimulate new formation of elastic tissue.

As a final note on the stroma of argentaffinomas it should be pointed out that the amount of any one special element of the stroma varies from place to place and from tumor to tumor. Collagen fibers and reticulum are always present. The other elements are present to some degree in almost all instances, but any one may predominate in a given place. The type of fiber seems to depend in large part on the variety of normal tissue adjacent to the tumor.

Besides these characteristics of the argentaffinomas and their stroma, several features of the malignant type should be pointed out. The percentage of malignancy increases with advancing years. It might be supposed that these tumors have been present for very long periods before symptoms develop. For example, in a patient in Raiford's [7] series a malignant argentaffinoma was found at operation in a patient 16 years of age. It was located in the appendix and metastases were present in the mesentery. The only symptoms were those of chronic

appendicitis. It is interesting to speculate on the possibility that without operation this patient would have lived for many years before the symptoms usually associated with a malignant tumor in this location developed, by which time distant metastases might have been present. In the two cases showing malignancy in the present series the patients are both at the upper limit of the age group, 57 and 64 years. Such tumors may have been developing for very long periods of time.

The cases of malignant argentaffinoma recorded in the literature (including the present ones) were distributed at the different levels of the gastro-intestinal tract as follows:

Stomach	2
Duodenum	0
Jejunum	2
Ileum	19
Small intestine (exact location not specified)	8
Appendix	7
Colon	2

Raiford [7] pointed out that benign argentaffinoma is much more common in the appendix than elsewhere with decreasing frequency at progressively more distant levels, so that the percentage of malignancy is lowest in the appendix and increases in proportion to the distance from that point. In his series, those of the stomach and colon were all malignant. However, the argentaffin tumors in these locations are so few that conclusions would be less definitive in respect to them than in respect to those in the appendix. The only argentaffinoma of the stomach in the series reported here was benign. None were found in the colon.

As judged from the two cases of malignant argentaffinoma studied, the mechanism of intestinal obstruction is different in these tumors from that of the usual adenocarcinoma of the intestine. The latter tumor produces narrowing of the lumen by growing entirely around the intestine in an annular manner with further constriction resulting from the contraction of the connective tissue in the stroma. The malignant argentaffinoma grows only a part of the way around the intestinal lumen (fig. 3) even though the external appearance of the unopened specimen, as in case 3, suggests an annular constriction (fig. 2). Low power microscopic examination (fig. 5) shows that the tumor growing from the mucosa into the submucosa and infiltrating the hypertrophied muscularis extends into the serosal layer. Here it forms a mass of tumor which has a dense stroma composed largely of collagenous fibers. The progressive contraction at this point causes a buckling of the overlying intestinal layers. There is formed in consequence a rounded mass, which projects into the lumen. The uninvolved intestine adjacent to the mass is puckered and distorted by this process with the result that the lumen is almost completely occluded. That this is the fundamental mechanism is suggested by the fact that in those tumors which

do not extend into the muscularis no distortion of the intestinal contour results. Furthermore, this same finding is present in cases in which intestinal narrowing is seen. In case 3, in which obstruction was almost complete, the extramuscular mass of tumor was larger than in case 2, in which the intestinal lumen was still functionally patent.

It should be pointed out that argentaffinomas show little or no ulceration. This is in contrast to the adenocarcinomas of the same location, which ulcerate extensively.

The mesenteric metastases, as seen in case 3 and as described repeatedly in the literature, occur characteristically outside lymph nodes, while these structures are invaded by smaller groups of actively proliferating tumor cells. Between the primary growth and the mesenteric metastases, as in case 3 and in the mesentery adjacent to the intra-intestinal growth in case 2, cords of tumor can be seen which infiltrate the fat freely. Many of these follow blood vessels and derive their stroma in part from the adventitia of such vessels. No evidence of lymphatic invasion was seen in this series.

Metastases are present in many cases beyond the limits of the mesentery. The nodules palpated in the liver at operation in case 3 were in all probability of such a nature. A tabulation of the metastases seen in cases reported in the literature (including the present cases) is as follows:

Mesentery (lymph nodes)	31
Liver	16
Cecum	1
Ileum	1
Peritoneum	1
Omentum	2
Pelvis	1
Lungs	1
Pleura	1

Lewis and Geschickter [8] advanced the theory that argentaffinomas are paragangliomas of the gastro-intestinal tract, differing only in location from paragangliomas of the suprarenal gland or carotid body. There are certain considerations which make such a view at least improbable. The Kultschitzky cells are entodermal or possibly mesodermal derivatives with little evidence pointing to an ectodermal origin. As seen in this study, given fields in benign and malignant argentaffinomas are histologically very similar, the differentiation being only on the behavior of the tumor. Lewis and Geschickter's statement on paragangliomas of the suprarenal gland is: "In the malignant forms giant, atypical ganglion and large spindle cells are found. Malignant paragangliomas are remarkable because of the size and variety of the giant cells. Eisenberg and Wallerstein have said that the greatest imaginable irregularity in size and shape of the cells and nuclei is the most striking histologic feature." Such a picture is not seen in malignant argentaffinomas, regularity in cell type being notable. Paragangliomas do not possess

the characteristic stroma described in argentaffin tumors. Masson [15] considered the argentaffinomas as paragangliomas of a hypothetic entodermal system and hence not in any way related to ectodermal tumors. The evidence points strongly to a place apart for the argentaffinomas, a grouping with tumors elsewhere in the body appearing impossible at the present time.

The clinical manifestations of argentaffin tumors are of some interest. The benign type except for those in the appendix are absolutely asymptomatic. The remarkable freedom of these tumors from ulceration and their small size contribute to this. In the series reported here no instance of intussusception resulting from an argentaffinoma was encountered, and the literature examined yields no report of such a case. It is beyond the scope of this paper to discuss the production of an internal secretion by the Kultschitzky cells or by the tumors arising from them. However, in the cases studied, the tumor was associated with disease of the endocrine glands only once, in that instance with tuberculosis of the suprarenal glands. Tumors made up of cells sufficiently differentiated to contain specific granules might be expected to function if they arise from endocrine tissue. No evidence of such disturbance could be found.

When the appendix is the site of an argentaffinoma, whether benign or malignant, symptoms are present which are not encountered in association with these tumors elsewhere. The patient has attacks of dull pain in the right lower abdominal quadrant which may be associated with acute manifestations, such as sharper pain, nausea and vomiting without fever or leukocytosis. Masson [16] described this syndrome as "neurogenic appendicitis." He pointed out that small neuromas are found in a high percentage of cases of so-called chronic appendicitis. This finding was confirmed by Hosoi.[17] Furthermore, Masson [6a] stated the belief that these neuromas form an integral part of the development of the argentaffinomas. It is difficult to see why a similar process at a different level would be so entirely asymptomatic. However, in this series, the tumors of patients J, L, M, R, S and U (table) belonged to this group. One might raise the question whether patient N was not benefited by the removal of the appendix instead of by the "major" part of the operation, consisting in the removal of lesions on the basis of which it is difficult to explain attacks of nausea and vomiting.

The malignant argentaffinomas produce symptoms very late. Ninety-two and five-tenths per cent were not discovered until lymph node or even more remote metastases were present. The clinical manifestations are those of chronic intestinal obstruction. As pointed out by Raiford,[7]

15. Masson, P.: Am. J. Path. **6**:217, 1930.
16. Masson, P.: Compt. rend. Acad. d. sc. **173**:262, 1921.
17. Hosoi, K.: Arch. Path. **16**:500, 1933.

diarrhea without melena is a frequent finding in the earlier stages. Indeed, one seldom sees the anemia so often associated with other types of malignant growth in the same location. The absence of ulceration in malignant as well as in benign argentaffinomas accounts largely for this finding. The intestinal obstruction is insidious, yet progressive. It allows time for tremendous dilatation of the proximal loops of bowel. In case 3 roentgenograms showed such a change (fig. 1). This was seen in several cases reported in the literature, notably that of Gáspár.[18]

The prognosis of malignant argentaffin tumors from a statistical review of the recorded cases appears to be decidedly unfavorable. However, the nature of the changes has been recognized in several cases only at postmortem examination, the location or even the presence of a malignant condition not being suspected during life. The tumors have a remarkably slow rate of growth. If found before remote metastases are present, the chance of recurrence will be much less than that of the usual adenocarcinoma in a similar location.

The treatment of malignant argentaffinomas must be surgical. A radical resection is indicated clearly in all cases without generalized metastases. When masses are found in the mesentery, these require excision of that sector with its attached intestine, often a meter or more. Such resection offers palliation for long periods of time even with metastases palpable in the liver, as in case 3. Because of the tendency of the argentaffinomas to invade the mesentery in cords very early, a constricting lesion of the gastro-intestinal tract which is recognized as a malignant argentaffinoma at the time of operation by its yellow color and by the peculiar method of growth described in this paper requires the resection of a sector of mesentery even in the absence of gross invasion. The percentage of cures in patients treated in this way will in all probability be very high.

SUMMARY

A series of thirty-one argentaffinomas of the gastro-intestinal tract is described. Three cases are presented in detail as representative of the various types of these tumors.

The stroma of the argentaffinoma consists of collagen fibers, reticulum, nerve fibers, smooth muscle cells and elastica. A study of the elastic tissue shows it to be abundant in both the benign and the malignant type of argentaffinoma. The metastatic tumor has a stroma composed of collagen, reticulum and elastic fibers. The elastica is derived in part from the adventitia of the small and medium-sized blood vessels in the tumor. The argentaffinoma has the property of stimulating the production of elastic tissue, a characteristic rare among tumors.

18. Gáspár, I.: Am. J. Path. **6**:515, 1930.

Intestinal obstruction results from the growth of the tumor in the serosal layer with consequent buckling and distortion of the tunica muscularis. In this series, at least, complete annular tumor growth did not occur.

Material is presented to show that the argentaffinoma cannot be regarded as a paraganglioma of the sympathetic nervous system.

Clinically, the argentaffinoma in any location except the appendix is characterized by its extremely asymptomatic course—throughout life if the tumor is benign; if malignant, until very late in the natural history of the tumor. With location in the appendix, the symptoms of acute or chronic appendicitis are simulated frequently. This is true whether the tumor is benign or malignant.

The extremely slow growth of the tumor of the malignant type encourages radical resection even in the presence of metastases. The tendency of the tumor to grow in cords in the mesentery renders it advisable to resect a segment of mesentery even in the absence of gross invasion.

Because of the asymptomatic course of the malignant tumors until very late, few have been subjected to early operation. Of those that did, very few have recurred.

ALLERGIC INFLAMMATION OF THE LUNGS

THE PATHOGENESIS OF LOBAR PNEUMONIA

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In previous articles I [1] have reported studies on the reaction of the lungs to bacteria and other substances in normal animals. The present contribution deals with the response of the lungs in animals that have been rendered allergic to a foreign protein.

MATERIAL AND METHOD

The experiments were conducted on full-grown rabbits fed on oats, hay, and green vegetables.

Five cubic centimeters of horse serum (diphtheria antitoxin) was injected intraperitoneally every sixth day over a period of forty-eight days, the amount of serum totaling 40 cc. On the sixth day after the last injection 1 cc. of serum was injected into the lung via the trachea. The technic of the operation has been described in a former publication.[2] The animals were killed from one hour to four weeks after the intratracheal ("shocking") injection.[3] The lungs fixed in situ were cut at different planes through the entire thickness, and sections stained with different dyes were studied.

OBSERVATIONS

Macroscopic Appearance.—The gross appearance of the lungs depended on the interval between the intratracheal injection and the death of the animal. When the rabbit was killed from eight to ten hours after the "shocking" injection, the surfaces of the lungs appeared normal. But when the thoracic cavity was opened from twelve to fifteen hours after the intratracheal injection, one lung (the right in the majority of cases) showed a smooth firm area of discoloration in the dependent portion of the lung and along the spinal column, resembling somewhat the paravertebral pneumonia occasionally seen in children. Of seventy-five rabbits used in the experiments, 60 per cent showed the following:

In some instances both lungs were of the same size; in others, either one whole lung or the lower lobe was somewhat shrunken, smooth and firm, while the

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From the Medical Division of the Montefiore Hospital.

This investigation was aided by a grant from the Emanuel Libman Fellowship Fund.

1. Fried, B. M.: Arch. Path. **3**:46, 1927; **6**:1008, 1928; **10**:213, 1930; **12**:689, 1931; **17**:76, 1934.

2. Fried, B. M., and Whitaker, L. R.: Arch. Int. Med. **40**:726, 1927.

3. The word "shocking" is not appropriate; it is used for want of a better term.

other lung was normally wrinkled, crepitant and collapsible. When placed in water the firm lung sank, pulling down its apparently normal fellow. A condition in which the size of one lung was reduced is shown in figure 1 *A* and *B*. From this illustration it may be seen that the lower lobe of the left lung is contracted, its base showing two areas of discoloration. It is noteworthy that the pulmonary surface was covered with fibrin, and that a sizable sterile fibrinous exudate, made up of

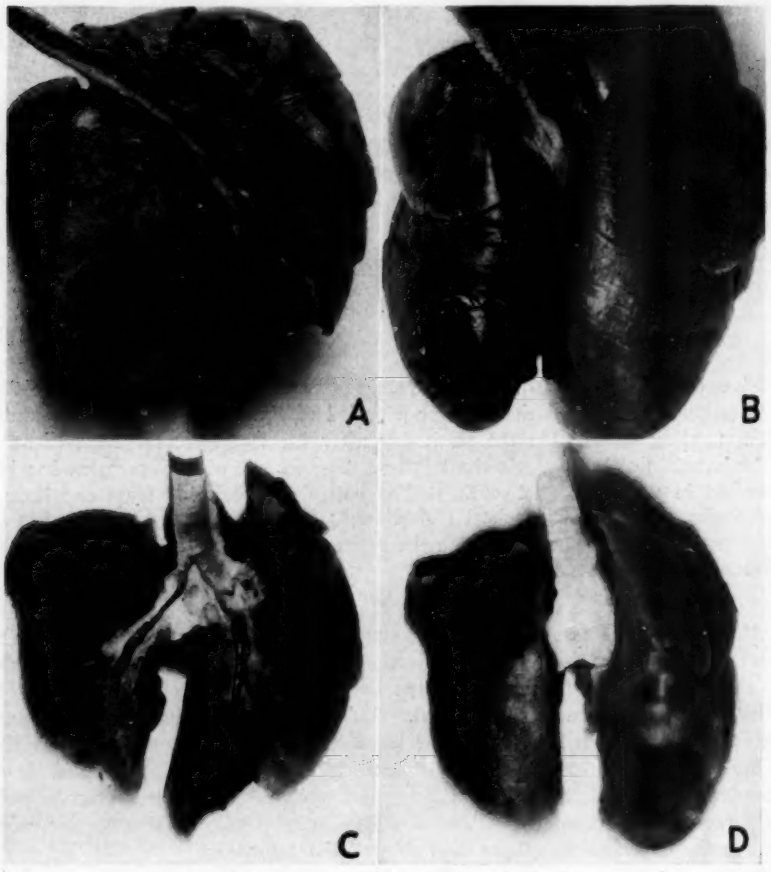

Fig. 1.—Pneumonic lungs. *A*, cut surface of the left lung; *B*, pleural surface of the same lung covered with fibrin; *C*, cut surface of the right lung; *D*, pleural surface of the same lung showing areas of discoloration (infarctions).

macrophages and granulocytes, was present in the pleural cavity. The cut surface of these lungs revealed "hepatization" of the left lung with a large hemorrhage—an infarct—in the lower segment of the organ (fig. 1 *A* and *B*). The picture resembled that of acute lobar pneumonia as seen in man.

Figure 1 *C* and *D* is illustrative of a group of animals in which the right lung was involved. In these cases both lungs were usually equal in size, but occasionally

the affected one was slightly larger (fig. 1 *C* and *D*). Nearly all these animals showed wide subpleural hemorrhages (infarctions). The cut surface of the lungs of the rabbits killed two and four days respectively after the injection of the "shocking" dose is demonstrated in figure 2. In these animals the left lung showed uniform consolidation of nearly half of the lower lobe, while the right lung was normal. The affected areas in both of the lungs were vaguely demarcated, and their cut surfaces were finely granular. The color of the lungs varied; the lesion of two days' duration was dark red, while the four day lesion was grayish white, showing evidence of a healing process.

Microscopic Examination.—Microscopically, the response of the parenchyma to the "shocking" dose was conspicuous within one hour. The lesion was that of an exudation of granulocytes and serum into the alveoli leading to their distention. The septal capillaries showed marked congestion and a large number of polymorphonuclear leukocytes mingling with erythrocytes. The reaction rapidly increased in intensity, and after three or four hours granulocytes flooded the lung,

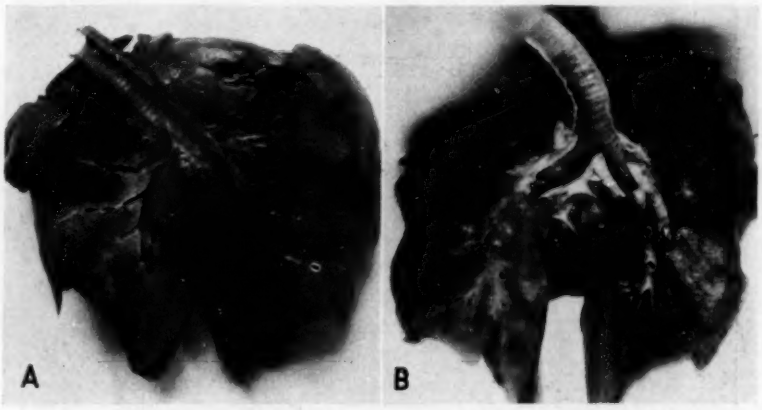

Fig. 2.—Cut surface of the pneumonic lungs. *A*, lungs removed from an animal killed two days after the "shocking" injection of serum; *B*, lungs removed four days after the "shocking" injection. In both cases the left lung is affected.

resulting in a tremendous dilatation of the air sacs. A thickening of the septums resulted from the massive accumulation of leukocytes and the swelling of the alveolar "epithelial" cells. Because of the abundance of the cellular exudate the normal markings of the lungs were obliterated in many areas. Insular atelectasis also occurred. That the cells were brought to the lungs by the circulating blood was apparent from their overwhelming numbers in the capillaries and larger blood vessels. The small vessels were plugged with granulocytes, squeezing out the erythrocytes.

A rapid disintegration of leukocytes was found in the lung of animals that were killed about twenty-four hours after the injection of the "shocking" dose. Wide areas of these cellular débris could be seen enmeshed in a coarse network of fibrin. At this time the lungs of a large number of animals contained an exudate composed of two varieties of mononuclear cells: macrophages (alveolar "epithelial" cells) detached *en masse* from the septums, and large eosinophilic cells apparently brought with the circulation (fig. 3 *A*). In a few instances the latter

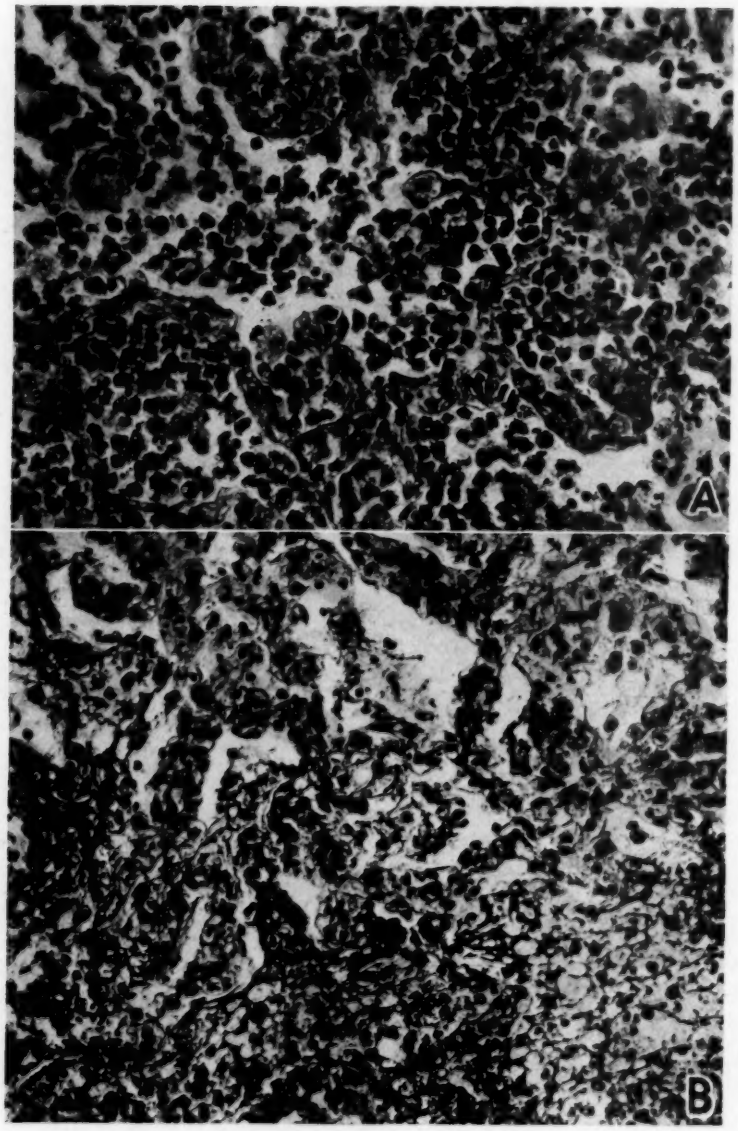

Fig. 3.—*A*, exudate in the pneumonic lung; *B*, meshwork of fibrin containing entangled mononuclear cells and disintegrated granulocytes.

cells dominated the picture. The alveolar macrophages were occasionally in mitoses and proliferated along the septums forming in places continuous files.

Fibrin began to appear in from twenty to thirty hours after the injection of the "shocking" dose, reaching its acme in approximately forty-eight hours (fig. 3 *B*).

Fig. 4.—Condition of a blood vessel found in the midst of the pneumonic parenchyma. The animal was killed twenty-four hours after the intratracheal ("shocking") injection of horse serum.

At that stage markings in the lungs were largely obliterated. There was a coarse meshwork of fibrin in which "corpses" of granulocytes were entangled, while the far more numerous mononuclear cells appeared to be rather normal.

The duration of the reaction paralleled the amount of pulmonary tissue involved. For example, in the rabbits (about 20 per cent) in which the inflammatory process

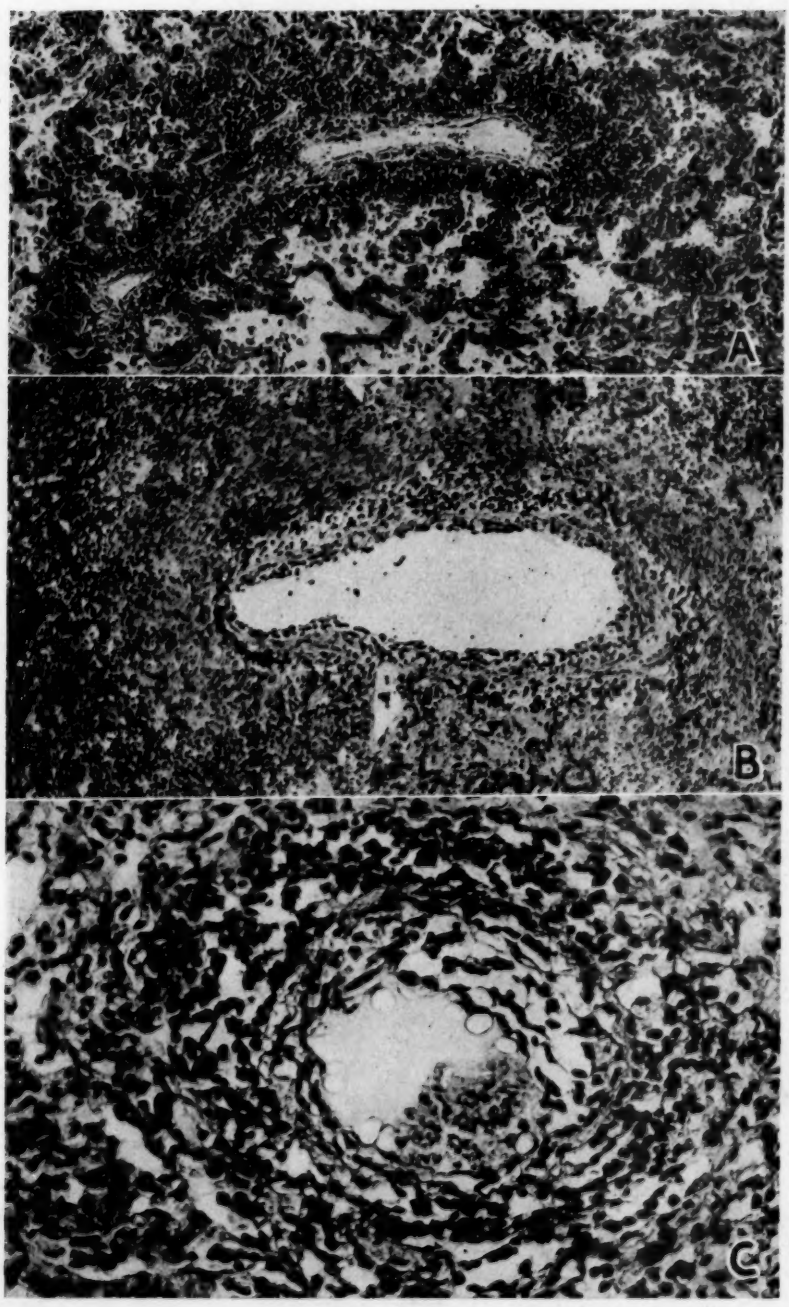

Fig. 5.—Different degrees of vascular changes. Section of the lung from an animal killed (*A*) two days, (*B*) three days and (*C*) four days following the "shocking" injection.

occupied an area from 1.5 to 3 cm. in diameter the exudate began to fade on the fourth day. In rabbits in which the lesion involved an entire lobe, pneumonic foci could be detected from eight to ten days after the injection of the "shocking" dose. In many animals the exudate disappeared entirely without leaving any traces, while in others, areas of organization were noticed on the fifth, sixth and seventh days after the "shocking" injection of the serum.

Blood Vessels.—The vascular system of the affected lung responded to the "shocking" dose as promptly as the parenchyma. The endothelial cells lining vessels of different caliber usually showed swelling and separation from the walls, singly and *en bloc*, thus adding to the overcrowded vascular bed containing excessive numbers of erythrocytes and granulocytes mingled with monocytes and occasional eosinophils. The walls of the vessels showed edema, and particularly remarkable was their early invasion by cells from within and without, leading to destruction of the architecture of the blood vessels. The almost complete occlusion of numerous small vessels by immigrated round cells and granulocytes has been described. Within a few hours after injection of the "shocking" dose of serum, numerous vessels showed fibrinoid changes of their walls. In many instances there was a proliferation of the intimal and subintimal layers causing thickening of the wall of the vessel, the newly formed tissue having a hyalinoid aspect. The adventitia of most of the vessels was surrounded by a cuff of mononuclear (monocytoid) cells, probably undifferentiated mesenchymal elements capable of transforming into monocytes and macrophages. Within the first few hours necrosis of the walls of the blood vessels (a vascularitis) was seen. The walls of the vessels were thoroughly infiltrated with myriads of cells, and it was surprising to find fibrin in the walls as well as in the lumens of the blood vessels. The presence of fibrin in the vascular lumens was a conspicuous trait in these cases. The picture of the pneumonic parenchyma and of the blood vessel shown in figure 4 is illustrative of the condition. There is an abundance of exudate made up of cells and serum. The perivascular lymphatics are distended and filled with cells. There is a great deal of fibrin. The wall of the vessel is permeated with cells which became "agglutinated," forming a nodule seen in the left upper segment of the picture (fig. 4). There is an abundance of fibrin in the lumen. Figure 5 shows changes in the wall of the vessel at different stages of the disease. In *A* there is a marked infiltration of the entire wall, somewhat resembling arteritis nodosa. In *B* (which shows a section of a lung removed from the thoracic cavity three days after the injection of the "shocking" dose), besides the cellular invasion of the wall of the vessel there is also a marked perivascular edema. In *C* the cellular infiltration forming a condition resembling a granuloma has finally led to complete dissociation of the wall of the blood vessel.

Infarctions extending to the pleura occurring early in the disease were conspicuous in many animals.

Bronchi.—The bronchial structures were found to be only mildly affected by the process, when compared with the gravity of the disease of the parenchyma and of the blood vessels. A peribronchial edema was present, but the bronchial walls showed no cellular infiltration, and the bronchial lining was intact.

COMMENT

The pulmonary reaction to small amounts of horse serum in rabbits sensitized with the same serum is remarkable in that there rapidly occurs an intense edema followed soon after by a spreading inflammation of the parenchyma and of the blood vessels, which in from twenty to

twenty-four hours involves one or more lobes of one lung and occasionally also the pleura. Similar or larger amounts of serum injected into the lungs of normal animals are usually lodged in the paravertebral regions of both lungs, which areas reveal a slight loss of their spongy appearance. In these animals the reaction of the lungs is slight; it occurs much later (about fifteen hours after the injection) and has a disseminated, insular character. In these cases the moderate exudate is composed of serum and granulocytes mingled with an occasional macrophage, and the lungs show no noticeable alteration of their configuration. In these animals the lungs regain their normal structure in from thirty to forty hours after the intratracheal injection, whereas in the sensitized animals signs of healing make their appearance in five or six days.

The mechanism of local allergic or anaphylactic inflammation studied by several investigators resulted in the following observation: When an antigen is introduced into man or lower animals it diffuses widely and rapidly into the circulation and the tissues, resulting in the formation of antibodies which can be detected in vitro by a specific precipitation test. But if animals are repeatedly treated with the same antigen (bacteria or foreign protein), the absorbing capacity of the antigen diminishes with each subsequent injection. Moreover, when the immunization is pursued, most of the antigen no longer disseminates, remaining at the site of injection, and, as in the experiments reported, causes a local acute exudative inflammation (Arthus' phenomenon). It is believed that local anaphylactic inflammation, like the general form of this manifestation, represents an altered capacity of the sensitized cells to react to the homologous antigen. The hypothesis was expressed that this type of inflammation occurs as the result of an interaction between the antigen and antibodies producing a toxic substance, a precipitin, according to Opie.[4]

The remarkable feature in the experiments here presented is that in a large percentage of cases the inflammation was confined to one lung, having a lobar distribution. The unilateral topography of the lesion is noteworthy because in control animals treated similarly with serum and dyes respectively the injected material invariably reached both lungs, setting up a mild inflammation in them.

Not only the topography but also the microscopic features of the inflamed lung are remarkable. Thus in a number of instances the pleura too was involved; the exudate composed in the first stages of serum and granulocytes was supplanted in from twenty-four to thirty hours by large mononuclear cells which crowded the alveoli and the septums. There occurred a widespread necrotizing arteritis, an abundant collection of fibrin and occasional infarctions. In animals killed about twenty-

4. Opie, E. L.: J. Exper. Med. **39**:659, 1924.

four hours after the intratracheal injection, the pulmonary lesion resembled in many respects that of acute lobar (genuine, fibrinous) pneumonia as seen in man.

In the period preceding Pasteur the cause of lobar or fibrinous pneumonia was attributed to chilling—frigus ("Frigus unica pneumoniae cause [The sole cause of pneumonia is chilling]"). With the advent of the bacteriologic era and the discovery of Diplococcus lanceolatus, "bacterium" took the place of "frigus," and the notion was prevalent that the penetration of the micro-organism into the lower portion of the respiratory tract is alone responsible for the disease.

However, it soon became apparent that another factor besides the micro-organism is essential in setting up the malady. The view was expressed that the host, too, plays a rôle in the initiation of the pulmonary inflammation ("disposition" to the disease). This hypothesis was soon corroborated in experimental studies (Welch,[5] Beco,[6] and Rasquin[7]). In recent reports Stillman[8] stressed the observation that "Pneumococci which have reached the lung as a result of inhalation usually disappear within a few hours and give rise to no infection. . . . The experiments indicate that even in so susceptible an animal as the mouse, other factors than the presence of the pneumococci in the lung are necessary for infection." Stuppy, Falk, and Jacobson[9] found that

> the intratracheal inoculation of Macacus rhesus and Cebus capucinus monkeys with varying amounts of virulent type I pneumococci did not result in lobar pneumonia, although in most cases it caused an increase in temperature and a leucocyte reaction, with a pneumococcus septicemia. Recovery usually occurred within a week after inoculation.

Stuppy and Falk[10] noted that in rabbits

> the intrabronchial insufflation with pneumococci of uniformly high virulence gave rise to a bronchopneumonia which usually caused death in two to five days, with septicemia and a generalized distribution of pneumococci in the lung. In some animals there occurred acute inflammation of the interstitial tissue of the lung and perivascular and peribronchial lymphangitis. Suppurative bronchitis and pleuritis were only occasionally seen.

I[1] have observed that a dose of pneumococci that kills a rabbit in approximately eighteen hours after injection into the blood stream causes the death of another rabbit in four days following intratracheal

5. Welch, William H.: Bull. Johns Hopkins Hosp. **3**:125, 1892.
6. Beco, L.: Arch. de méd. expér. et d'anat. path. **13**:51, 1901.
7. Rasquin, E.: Arch. de méd. expér. et d'anat. path. **22**:864, 1910.
8. Stillman, E. G.: J. Exper. Med. **38**:117, 1923.
9. Stuppy, G. W.; Falk, I. S., and Jacobson, M. A.: J. Prev. Med. **5**:81, 1931.
10. Stuppy, G. W., and Falk, I. S.: J. Prev. Med. **5**:89, 1931.

inoculation. On the other hand, a dose of this micro-organism causing the death of a hematogenously infected animal in from three to four days is harmless to an animal inoculated via the respiratory tract. In no instance could I induce an acute lobar inflammation of the lungs.

Briefly stated, lower animals resist the experimental induction of lobar pneumonia. The reason was not explained. Obscure, too, is the reason why in man the pneumococcus frequently causes a patchy (insular or miliary) bronchopneumonia scattered in both lungs, having a gradual onset, a protracted course and a "lytic" termination, while in other cases the same micro-organism initiates a disease with a rather sudden onset and abrupt termination ("cyclic" course), the lesion being lobar and unilateral.

Wadsworth [11] called attention to the fact that in animals that have been incompletely or partially immunized to the pneumococcus a subsequent infection with highly virulent pneumococci injected intratracheally causes a lesion akin to human lobar pneumonia. He noticed that in these cases the virulent micro-organism does not disseminate throughout the body and cause septicemia but remains fixed in the lungs, producing an acute lobar lesion.

Formerly observers were uncertain as to whether lobar pneumonia originates primarily in the respiratory organs or is a blood-borne condition which has "settled" in the lungs. The consensus today is that the disease is effected through inhalation, by way of the upper respiratory tract, of Diplococcus lanceolatus, rarely of Diplococcus mucosus, staphylococci or streptococci. The disease starts most likely in the parenchyma of the lung, namely, at the periphery of the acinus (and not in the bronchioles), from which it spreads toward the surrounding parenchyma *per continuitatem* by way of the lymphatics, toward the hilar lymph nodes, and also possibly by way of the bronchioles (canalicular spread), stimulated by coughing. The process, as it is known, usually involves one lung, and, as a rule, is confined to one lobe. From this observation the inference was that the rapidly spreading inflammation limited to one lung results probably from the fixation in situ of inhaled pneumococci in the previously sensitized pulmonary tissue, or that it is a local allergic manifestation. It was pointed out that lobar pneumonia occurs rarely, if at all, in babies under 5 months of age, that cases of fibrinous (genuine) pneumonia that have been reported to have occurred in infants in the first few months of life were usually traced to a transplacental transmission of the hypersensitivity and of the disease from the mother at the time of delivery. It has been stated that the resistance of babies to genuine pneumonia is due to the fact that they had no opportunity of becoming infected and are therefore

11. Wadsworth, A.: Am. J. M. Sc. **127**:851, 1904.

relatively immune. Thus the "virgin" lung of the baby, like that of the normergic lower animal, rapidly disposes of the pneumococcus when it is inhaled for the first time without undergoing an acute lobar inflammation. On the contrary, in a lung that has been sensitized on previous occasions a minimal number of pneumococci is likely to cause a massive involvement.

I have quoted the experiments by Wadsworth to this effect. His work was repeated with contradictory results. For example, Stillman and Branch [12] found that "mice which have been partially immunized by previous inhalations of living or killed pneumococci and while alcoholized are exposed to an atmosphere of virulent pneumococci often develop a pneumococcus lobar pneumonia." Stuppy, Cannon and Falk [13] succeeded in inducing an acute exudative lesion in the lung of partially immunized rabbits.

Sharp and Blake [14] noted that in rabbits rendered hypersensitive to the pneumococcus, a subsequent intrabronchial insufflation of this micro-organism caused an acute inflammatory reaction of the lung in a number of instances. Lindau [15] found that "sterile pneumococcus autolysate, injected intratracheally into guinea-pigs with positive skin test, caused pulmonary reactions with lobar tendency." Lauche [16] detailed in many articles the allergic conception of genuine pneumonia of which he is a follower. In his studies of a large number of pneumonic human lungs Loeschke [17] found that the inhaled pneumococci "set up a hyperergic reaction in a sensitized allergic organism." According to the observations of this author the hyperergic (allergic) reaction causes at the point of inoculation an abundant edema in which the pneumococci proliferate with great rapidity. The exudate rich in pneumococci spreads throughout the lung by way of the interalveolar pores, setting up in the newly invaded alveoli an allergic type of response.

It is noteworthy that by intratracheal injection of egg albumin or of pneumococcus protein Julianelle and Roads [18] succeeded in inducing an inflammatory reaction in the lungs of rabbits previously inoculated with the respective antigen. They also found that a similar reaction occurs following an intratracheal injection of pneumococcus protein into the lungs of rabbits previously inoculated with heat-killed suspensions of the bacteria. However, their experiments "failed to show that hyper-

12. Stillman, E. G., and Branch, A.: J. Exper. Med. **54**:623, 1931.
13. Stuppy, G. W.; Cannon, P. R., and Falk, I. S.: J. Prev. Med. **5**:97, 1931.
14. Sharp, E. A., and Blake, F. G.: J. Exper. Med. **52**:501, 1930.
15. Lindau, A.: Acta path. et microbiol. Scandinav. **10**:1, 1933.
16. Lauche, A., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, p. 915.
17. Loeschke, H.: Beitr. z. path. Anat. u. z. allg. Path. **86**:201, 1931.
18. Julianelle, L. A., and Roads, C. P.: J. Exper. Med. **55**:797, 1932.

sensitiveness to pneumococcus or its products influences the occurrence or character of the lesion in the lungs in artificial pneumococcus infection."

In a recent article Cole [19] treated another aspect of the problem. He wrote:

> With increasing experience, it becomes more and more evident that pneumonia rarely arises primarily through infection with the organisms responsible for the pneumonic lesions, but that for these organisms to induce infection the soil must be prepared, probably by some other less serious infection, usually one involving the upper respiratory tract.

This "dualistic" conception of the pathogenesis of lobar pneumonia was supported by "careful investigation which shows . . . that many patients with pneumonia exhibit symptoms referable to the upper respiratory tract for a longer or shorter period before the onset of the disease itself" (Cole). Indeed, it is possible that the preceding "less serious infection" produces a nonspecific sensitization of the lung toward the pneumococcus. It may also be that the "upper respiratory" disturbances preceding lobar pneumonia are none other than premonitory symptoms of the disease "smoldering" in the lung, for the clinical onset of the disease in genuine pneumonia, as in other morbid conditions, does not coincide with the moment of infection. The abrupt onset of lobar pneumonia seen in many patients usually coincides with a rather considerable involvement of the lung and often also of the pleura. It should be remembered that the lung remains "solid" for a considerable length of time after the apparent (clinical) cure of the disease.[20]

In this respect it is of interest to note that the reaction produced by the final injection of the protein into sensitized animals was designated by writers as "shocking," "fulminating" and "explosive," the inference being that it is akin to the general anaphylactic shock, which was compared by Besredka to an explosion produced by an abrupt pouring of water into sulphuric acid. Indeed, if tissues are examined from twenty-four to forty-eight hours after the final injection of the antigen, the impression is gained that an "explosion" has occurred because of the profound alteration of the tissues in and around the area of injection. In reality it takes from fifteen to twenty-four hours for the local allergic inflammation to attain its height. This holds true of the lungs as well as of the cutaneous lesion produced by Arthus.

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19. Cole, Rufus: Canad. M. A. J. **30**:237, 1934.

20. Since "time immemorial" alcohol was considered an important factor in the contraction of lobar pneumonia. This was not investigated seriously; it has never been established that the disease occurs with greater frequency in alcoholics. Moreover, as in the case of the "upper respiratory" disturbances, it is not unlikely that the "intoxication" merely coincided with the onset of the malady at the time when it showed no demonstrative clinical manifestations.

It is important to stress that, unlike experimental infection, natural infection by way of the respiratory tract usually occurs with small amounts of bacteria which cause no disease in the normergic lower animal and in all likelihood in the normergic person. But in the allergic subject small quantities of bacteria produce the hyperergic type of inflammation, just as in sensitized animals small amounts of serum produce the acute lesion heretofore described. Moreover, as stated, a general systemic dissemination is prevented; that is, the organism remains fixed in situ.

SUMMARY

When an antigen is repeatedly injected subcutaneously into an animal, its absorbing capacity diminishes with each subsequent injection. Moreover, in these cases the last injection (usually the fifth or sixth) produces an acute exudative inflammation locally, looked on as an anaphylactic phenomenon; it is assumed that it occurs as a result of a combination of antigen and antibodies.

In the experiments reported in this article rabbits were sensitized by repeated intraperitoneal injections of horse serum, the last injection (defined as "shocking") being introduced into the lungs via the trachea.

A study of the lungs of these animals showed that: 1. The intratracheal ("shocking") injection of the heterologous serum soon produced an acute exudative, rapidly spreading inflammation in the lungs. 2. In a high percentage of the animals studied the lesion at its height was confined to one lung, having a diffuse lobar distribution. 3. The gross and microscopic aspects of the pulmonary lesion resembled in many ways acute lobar (fibrinous or genuine) pneumonia as seen in man.

The nature of the latter disease was analyzed, and the hypothesis was expressed (in accord with the views of earlier observations) that in this malady the character of the lesion in the lung probably depends on a state of local pulmonary hypersensitiveness (allergy, hyperergy).

The similarities between the lesions in the lungs in genuine pneumonia in man and those observed in the experiments with horse serum reported in this article (which should be regarded as "model" infections) favor this hypothesis.

EFFECT OF PARATHYROID EXTRACT ON THE BONES OF THE HYPOPHYSECTOMIZED RAT

A HISTOLOGIC STUDY

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Jaffe and his co-workers [1] showed that large doses of parathyroid extract lead to osteoclastic bone resorption in various experimental animals. Later Johnson [2] pointed out that he sometimes observed the formation of osteoid tissue in the bones of animals given this preparation. We have never seen osteoid formation as a result of overdosage of parathyroid extract in this laboratory, but we have regularly been able to stimulate the formation of fully calcified normal bone tissue by the chronic administration of this extract to rats. Some difference in the diet or in the caging conditions may perhaps account for this discrepancy between Johnson's observations and ours. Our studies of the more minute morphogenetic action of parathyroid extract on the osseous tissue have shown that it is necessary to differentiate between two entirely different types of bone reaction to the extract: the osteoclastic and the osteoblastic reaction.[3] Large doses of parathyroid extract lead to the proliferation of osteoclasts and simultaneously to bone resorption. When the daily administration of the extract is continued, the experimental animal, if it survives this stage, becomes gradually more and more resistant, and its clinical condition improves in spite of the continued treatment. During this stage of increased resistance the bone shows a disappearance of osteoclasts and proliferation of numerous osteoblasts, with formation of entirely normal, calcified new bone. If the treatment is started with a very small dose, one may even stimulate the formation of new bone tissue immediately, without a preliminary stage of bone resorption.[3a]

From the Department of Biochemistry, McGill University.

1. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Klin. Wchnschr. **9**:1717, 1930; J. Exper. Med. **55**:695, 1932.

2. Johnson, J. L.: Am. J. M. Sc. **183**:769, 1932.

3. Selye, H.: (*a*) J. A. M. A. **99**:108, 1932; (*b*) Endocrinolology **16**:547, 1932.

Since the pituitary growth hormone is considered to be essential for the growth of the skeleton and hypophysectomy stops growth, we have been interested to see whether the formation of osseous tissue by treatment with parathyroid extract, as observed in our previous experiments, is also dependent on the presence of the hypophysis. In order to study this question, we hypophysectomized twenty male rats, from 40 to 50 days of age, thirteen of which we treated with graded daily doses of parathyroid extract, starting with 1 unit on the first day and increasing the dose by 1 unit every day until the eighth day, after which they received 8 units daily. The remaining seven animals were used as controls, and intact treated and untreated animals of similar

A shows the lower end of the femur of an albino rat twenty-six days after hypophysectomy. Note the poor development of the trabeculae in the subepiphyseal region. *B* shows the lower end of the femur of an albino rat hypophysectomized twenty-six days before and since then treated with small doses of parathyroid extract.

age were also studied. Two animals of each group were killed on the eighth day of treatment; at this period the hypophysectomized rats showed marked bone resorption with the formation of numerous osteoclasts, while the normal animals receiving the same treatment already showed new bone formation and proliferation of osteoblasts. The remaining animals of both groups were killed in pairs between the twelfth and the twenty-fifth day of treatment. While the bone apposition was always much more marked in a normal animal than in its hypophysectomized control, it became obvious that in a later stage—

from the fourteenth day on—the hypophysectomized animals also began to show proliferation of osteoblasts and formation of new bone. This became marked in animals killed during the third week and later.

From these experiments we conclude that parathyroid extract may stimulate the formation of bone tissue even in the absence of the hypophyseal growth hormone.

In this connection we should like to emphasize a few facts which we believe are important for the understanding of the mechanism of the action of the growth hormone. We have observed that compensatory hypertrophy of the remaining kidney occurs in hypophysectomized rats after unilateral nephrectomy; furthermore, Dr. Jeffers has found in this laboratory that mitotic figures are plentiful in the mammary glands of hypophysectomized rats at the time of parturition. It is also well known that the proliferation of fibroblasts and epithelial cells in wound healing is not seriously interfered with by hypophysectomy, and that transplanted tumors grow, though less rapidly than usual, in hypophysectomized rats. All of these observations show that the proliferation of cells and the growth of individual organs are not necessarily dependent on the growth hormone. That animals may survive hypophysectomy for several years shows distinctly that cells of the various organs which died during this period have been replaced by new ones. The present paper shows that even a generalized growth (although not increase in length) of the osseous system may be produced in the absence of the pituitary growth hormone.

We conclude that the growth of the various organs in themselves is largely independent of the hypophysis. Apparently the function of the pituitary growth hormone is only to permit enlargement of the size of the body as a whole, with a harmonious and proportional increase in the size of all the organs.

Eli Lilly & Co. supplied the parathyroid extract used in these experiments.

DI-NITROPHENOL

STUDIES OF BLOOD, URINE AND TISSUES OF DOGS ON CONTINUED MEDICATION AND AFTER ACUTE FATAL POISONING

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In connection with the therapeutic use of 2, 4, di-nitrophenol [1] it appeared desirable to determine what changes, if any, in vital functions and organs might be produced by prolonged administration of doses comparable to the clinical ones and by acutely fatal doses. Tainter and Cutting [2] have reported briefly the somewhat indefinite histologic changes observed after the injection of large or fatal doses into dogs for periods of about one month. Schulte and Tainter [3] observed no harmful effects on the function of the kidneys in rabbits medicated for seventy-seven days. In the present report, the effects of nonfatal doses administered to dogs daily for six months are described.

METHODS

Nine adult male dogs were kept in large cages and fed all they would eat of a balanced commercial dog food. In addition, they were given cod liver oil and frequent exercise outdoors in the sun. The experiment was started after a period of quarantine of one month. Each week, three of the dogs were weighed and placed in separate metabolism cages, and quantitative collections of urine were made for twenty-four or more hours. During this period, samples of blood of from 10 to 15 cc. were obtained from each dog, using a vein of the leg. The urine was examined for sugar by Benedict's qualitative method and for albumin by the

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2. Tainter, M. L., and Cutting, W. C.: J. Pharmacol. & Exper. Therap. **49:** 187, 1933.

3. Schulte, T. L., and Tainter, M. L.: Proc. Soc. Exper. Biol. & Med., **31:** 1163, 1934.

quantitative method of Shevky and Stafford.[4] The samples of blood were used for determination of: the hemoglobin content in grams per hundred cubic centimeters, using the acid hematin method and a fixed glass standard in the Klett colorimeter; the red, white and differential cell counts by the usual clinical methods; the blood urea by the urease method, and the icteric index of the plasma against a fixed glass standard in the colorimeter. Before reading the icteric index, the di-nitrophenol in the serum was decolorized by dilution with tenth-normal hydrochloric acid. Preliminary observations showed that the acid did not alter the color of the bile pigments in the serum and hence did not change the icteric index when no drug was present.

After a control period of six weeks, dogs A, D and G were designated as control animals; B, E and H were given 5 mg., and C, F and I, 10 mg., of di-nitrophenol per kilogram of body weight, orally in capsules, daily for six days in each week. The average daily therapeutic dose for man is about 3 mg. per kilogram; so the dogs received up to about three times the usual clinical dose. Dog E, receiving 5 mg., was killed in a fight in the middle of the experiment. The others remained in apparent good health during the twenty-seven weeks that the drug was given. At the end of the twenty-fourth and of the twenty-seventh week, the oxygen capacity of the blood was determined by means of the device described by Anrep and Harris,[5] and the fragility of the red blood cells was determined by their resistance to hypotonic salt solutions.[6] Then the experiment was discontinued, and the dogs were killed for histologic study of the tissues. Each dog was killed by injecting a solution of a cyanide salt intravenously, and a complete necropsy was performed. The brain was removed at the moment of death, and one half was fixed in alcohol and the other half in a neutralized solution of formaldehyde made isotonic with potassium bromide.

CLINICAL RESULTS

The results may be discussed according to the tissue, fluid or function studied.

Body Weight.—The average initial weight of the three control dogs was 8.3 Kg., and the average weight at the end of the experiment was 9 Kg., a gain of 0.7 Kg. The two dogs receiving 5 mg. daily, which survived for six months, weighed at the beginning of administration of the drug an average of 9 Kg., and at the end, 8.4 Kg., a loss of 0.6 Kg. The three dogs given doses of 10 mg. started with an average weight of 12.5 Kg. and ended with an average weight of 12.8 Kg., a gain of 0.3 Kg. These results show that there were no important changes in body weight as a result of the continuous administration of di-nitrophenol during six months, under the conditions employed.

Urinary Protein and Sugar.—No sugar was found in the urine of any of the dogs throughout the entire period of medication. The changes in the output of urinary protein in twenty-four hours are shown graphically in chart 1. The highest daily output during the control period was 75 mg. Dog H, given doses of 5 mg. of di-nitrophenol, excreted up to a peak of 142 mg. of albumin during the twelfth week of medication, but the excretion fell to the control level of 12 mg.

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4. Shevky, M. C., and Stafford, D. D.: Arch. Int. Med. **32**:222, 1923.

5. Anrep, G. V., and Harris, D. T.: Practical Physiology, London, J. & A. Churchill, 1923, p. 99.

6. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, ed. 6, Philadelphia, W. B. Saunders Company, 1928, p. 363.

at the end of the experiment, when the drug was still being given. Dogs F and I, given doses of 10 mg. of di-nitrophenol, showed a similar increase in the protein output at the same time, but a return to normal levels occurred while the drug was still being given. At the time of the greatest excretion of albumin the urine gave only a faintly positive reaction with heat and acetic acid; so the changes, although

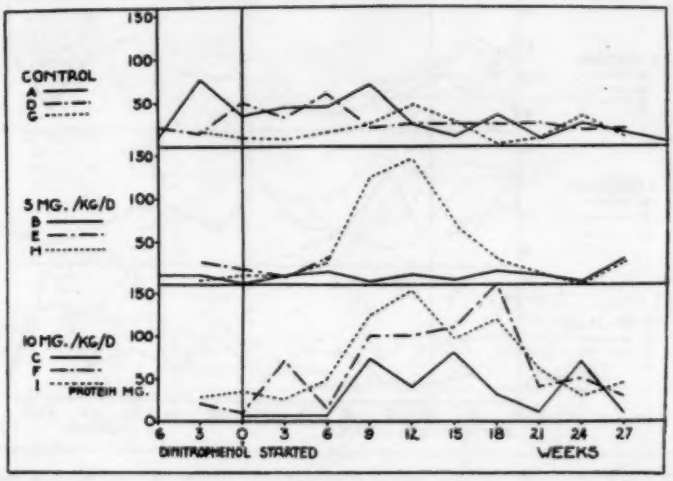

Chart 1.—Effects of di-nitrophenol administered orally on amount of albumin in the urine of dogs in twenty-four hours. In this and the following charts, each line represents one dog, and Mg./Kg/D indicates the dose of di-nitrophenol in milligrams per kilogram per day.

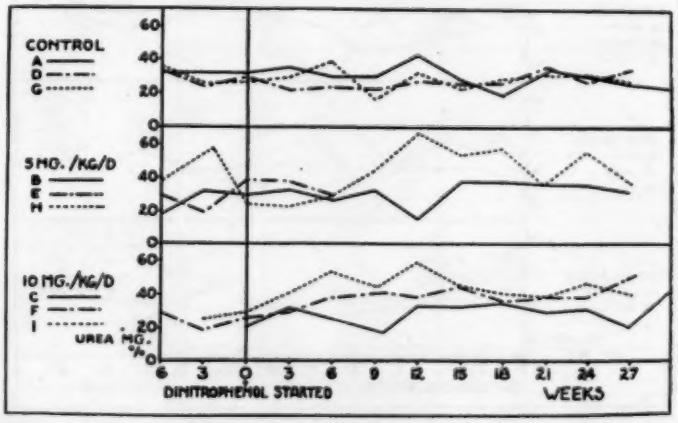

Chart 2.—Effects of di-nitrophenol administered orally on the blood urea concentration of dogs.

definite, were not of sufficient magnitude to be important in the absence of other evidence of renal damage. The fact that the final values were all in the normal range also indicates that the di-nitrophenol did not cause progressive damage of the kidneys but that the temporary increase in the albumin content was possibly due to some intercurrent factor.

Blood Urea.—The absence of significant renal damage was confirmed by the practically negative results of determinations of the blood urea. In chart 2 it may be seen that there was no consistent change in the level of this blood constituent during the period of medication. Hence, the kidneys were not functionally damaged, according to this test.

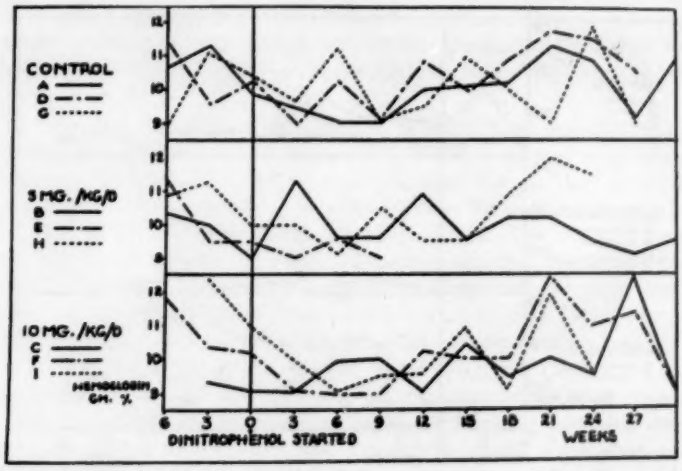

Chart 3.—Effects of di-nitrophenol administered orally on the hemoglobin content of the blood of dogs.

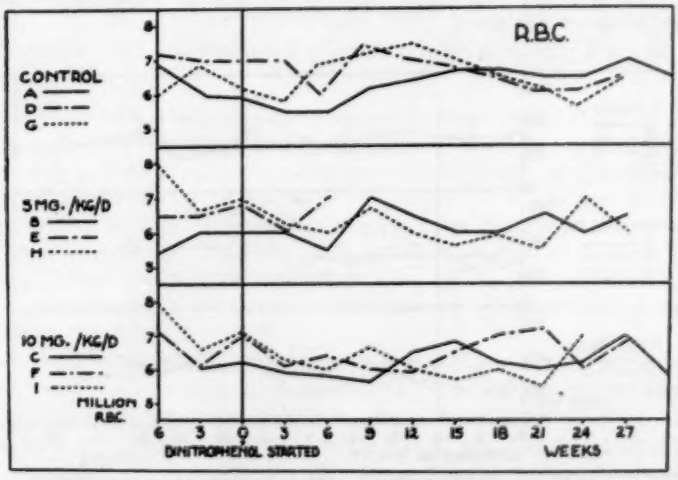

Chart 4.—Effects of di-nitrophenol administered orally on the red blood cell count of dogs.

Hemoglobin and Red Blood Cells.—The hemoglobin content of the blood was found to be rather variable. This was undoubtedly due partly to difficulties in the method, since some trouble was experienced at times because of a poor color match with the standard. The average results (chart 3) indicated no significant change in the concentration of hemoglobin. Counts of the red blood cells also showed no

significant change (chart 4). At the end of the twenty-fourth week of the administration of di-nitrophenol and again at the end of the twenty-seventh week, the oxygen capacity and the fragility of the red cells were determined. The control dogs gave an average value of 14.5 per cent by volume for oxygen capacity;

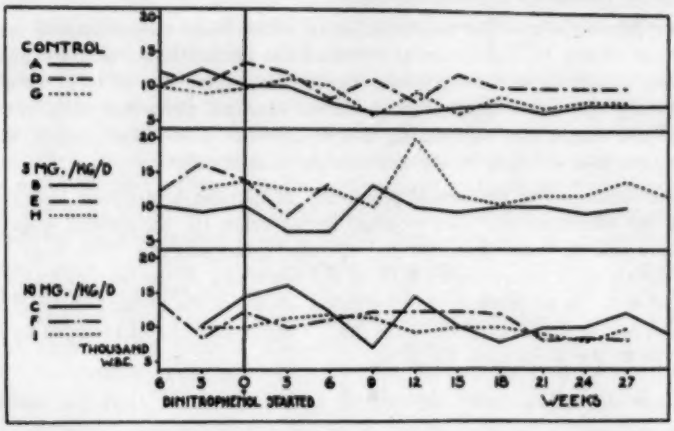

Chart 5.—Effects of di-nitrophenol administered orally on the white blood cell count of dogs.

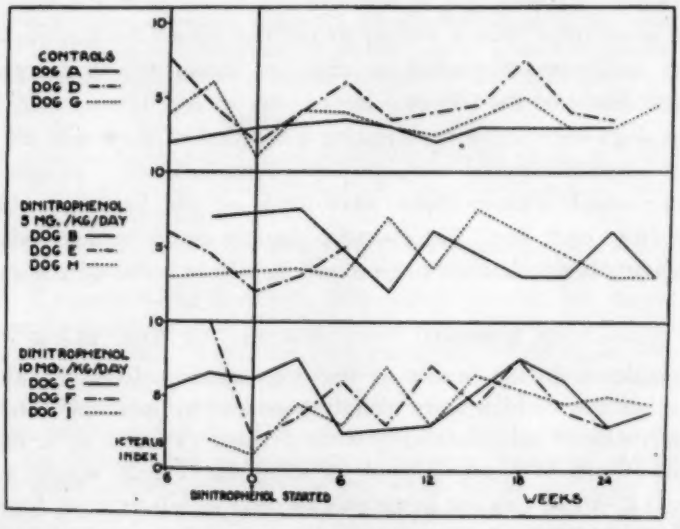

Chart 6.—Effects of di-nitrophenol administered orally on the icterus index of the blood serum of dogs.

the dogs given 5 mg. doses, 15.3 per cent, and those given 10 mg. doses, 16.1 per cent. The individual values ranged between 13.5 and 18 per cent. Accordingly, it appears that di-nitrophenol, if anything, increased slightly the average oxygen capacity of the blood; and, what is more important, there was no decrease.

In the fragility tests made at the same time, the results were very uniform. In all the dogs, hemolysis began with concentrations of the salt of 0.462 and 0.423 per cent and was complete with concentrations of 0.336 and 0.295 per cent. There was thus no alteration in the fragility of the red cells, as shown by their resistance to laking by hypotonic solutions.

White Blood Cells.—The total number of white blood cells remained unchanged throughout (chart 5). Differential counts from smears failed to show any alteration in the proportions of eosinophils, basophils, lymphocytes or large mononuclear or polymorphonuclear neutrophils. There were no abnormal cells present, as judged from shape, size or staining characteristics. The blood picture, therefore, remained normal throughout the six months of medication.

Icteric Index.—The theoretical possibility of damage to the liver led to observations of the icteric index. The average initial value for the control dogs was 3.7, and at the end of the experiment the average value was 3.3. The dogs receiving di-nitrophenol gave an average of 3.8 at the beginning of the administration and of 3.5 at the end. In no instance did the index go above the normal range during the administration of di-nitrophenol (chart 6). Therefore, this test revealed no evidence of damage to the liver from the drug.

Comment.—The tests described failed to show that six months of continuous oral administration of di-nitrophenol to dogs, in doses three or more times the clinical, produced any pathologic changes, unless such changes were indicated by the small increases in the amount of albumin in the urine. However, it is believed that the albuminuria was coincidental, since there was a return to normal values during medication. Further evidences of pathologic changes, therefore, were sought by histologic study of the tissues.

The dogs were killed by injecting a solution of a cyanide salt intravenously, and necropsies were performed immediately. Routine gross and microscopic examinations were made of the brains, tissues and organs from each dog. No essential changes could be detected in any of the animals which were not present in one or more of the controls.

CHANGES OBSERVED POST MORTEM IN THE BRAIN

In addition to the brains of the dogs already discussed, those of three other dogs which were acutely poisoned by injecting fatal doses of di-nitrophenol subcutaneously were studied. Two of these dogs had received 30 mg. of di-nitrophenol per kilogram of body weight, and one had been given 20 mg. per kilogram; all died within three or four hours from hyperpyrexia.

Immediately after death, the brains of both the chronically and the acutely poisoned animals were removed, and one half of each was fixed in 96 per cent alcohol and the other half in a 4 per cent solution of formaldehyde. After fixation blocks were removed from the frontal, motor, parietal, occipital and temporal regions, including the subcortical centers, as well as from the cerebellum, the medulla oblongata and the cervical portion of the cord.

The alcohol-fixed material was stained en bloc with methylene azure, embedded in paraffin and cut in sections from 15 to 20 microns thick. Paraffin sections of alcohol-fixed material were also stained with coelestin blue-eosin, chromium alizarine cyanin and alum-gallamin blue.[7] The fibrous and protoplasmic glia were stained by Cajal's method, and the microglia by Hortega's method combined with Herxheimer's fat stain. Spielmeyer's and Bielschowsky's methods were used for staining the myelin sheaths and axis-cylinders.

Sections of the various regions of the cortex of the acute and chronically poisoned animals, stained with methylene azure en bloc, showed the nerve cells intact, with the exception of a few sclerotic cells scattered throughout the cortical layers. Sclerotic cells were also found in the control animals and were probably due to senile changes. Hemorrhages and cellular infiltrations were found in dog H only, and were undoubtedly of infectious origin. The glia cells were unchanged, no regressive or progressive changes being demonstrable. A slight perivascular fatty infiltration was found in all animals, including the controls. The nerve and glia cells of the striatum and pallidum, the ganglion cells of the cornu ammonis and the Purkinje cells of the cerebellum and nucleus dentatus were all intact, as were the nuclei of the medulla oblongata. The cervical portion of the cord was normal. No changes could be demonstrated in the myelin sheaths or in the axis-cylinders.

CHANGES OBSERVED POST MORTEM IN OTHER TISSUES

The other tissues from the dogs used in the chronic feeding experiment were subjected to careful gross and microscopic examination. The specimens were fixed in Orth's and Zenker's fluids. Frozen sections were made of each tissue and stained with hematoxylin and sudan III for the demonstration of fatty changes. Parts of each tissue were embedded in paraffin, cut in sections 5 microns in thickness and stained with hematoxylin and eosin and hematoxylin and Van Gieson's stain. Bone marrow sections were stained with Giemsa's stain and hematoxylin and eosin.

The following protocols are arranged according to the dosage of di-nitrophenol.

Dogs Given 10 Mg. of Di-nitrophenol per Kilogram.—Dog C.—Grossly all the organs were essentially normal.

The results of microscopic examination were as follows: The liver was moderately congested throughout. The central veins and sinusoids were slightly dilated. The neighboring liver cells were slightly atrophic but showed normal cytoplasmic and nuclear staining. No fatty changes were observed. One testicle had a normal structure. In the other there was atrophy of the tubules with absence of spermatids and spermatocytes. There were no demonstrable changes in the interstitial cells. The lungs showed moderate congestion of the alveolar and septal capillaries and blood vessels. The heart presented slight atrophy of the muscle fibers. The thyroid gland was moderately congested. The acini were of normal size and shape and were filled with colloid which stained uniformly with eosin. The lymph nodes showed slight lymphoid hyperplasia. The islands of Langerhans were numerous but showed no abnormalities. The reticulum of the pulp of the spleen showed slight fibrous thickening and contained small amounts of finely granular brown pigment. The cells of the suprarenal cortex were heavily laden with lipoid. The kidneys were normal, with no changes in the tubules. The epididymis, stomach, intestines, bone marrow and skeletal muscles were normal.

Dog F.—Grossly all the organs were essentially normal.

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7. Proescher, F., and Arkush, A. S.: Stain Technol. **3**:28, 1928, Einarson, L.: Am. J. Path. **8**:293, 1932.

The results of microscopic examination were as follows: The liver showed normal architecture throughout. The central venules and sinusoids were moderately congested, but no fatty or degenerative changes were observed. In the lungs there was marked capillary congestion. The lymph nodes showed slight lymphoid hyperplasia. The islands of Langerhans were rather numerous and moderately congested. Scattered throughout the pulp of the spleen were small amounts of brown, granular pigment. The malpighian bodies were rather prominent, with their centers less dense than their peripheries. The cells of the suprarenal cortex were heavily laden with lipoid. There was moderate congestion throughout the suprarenals. The kidneys showed occasional tiny cortical scars and occasional small groups of round cells. In some of the convoluted tubules there was slight to moderate cloudy swelling of the lining epithelium. A few hyaline casts were contained in some of the collecting tubules. The glomeruli were normal. The kidneys were moderately congested throughout. The testicles, epididymis, heart, thyroid gland, stomach, intestines, bone marrow, skeletal muscles and parathyroid glands were normal.

Dog I.—Grossly all the organs were essentially normal.

The results of microscopic examination were as follows: The liver was markedly congested throughout. All the central sinusoids were greatly distended with red blood corpuscles. In some areas the central lobular cells showed marked atrophy. No fatty or hydropic degenerative changes were present. In the lungs the alveolar capillaries were markedly congested. In the thyroid gland nearly all the acini were filled with colloid, and many were rather large. The parathyroid glands were moderately congested. The lymph nodes showed slight lymphoid hyperplasia. Scattered throughout the pulp of the spleen were small amounts of brown, granular pigment. The malpighian bodies were prominent. The trabeculae showed slight fibrous thickening. The cells of the suprarenal cortex were heavily laden with lipoid. The kidneys showed marked congestion of the glomerular capillaries. In some of the convoluted tubules there was slight cloudy swelling of the epithelium. A few hyaline casts were contained in some of the collecting tubules. The testicles, epididymis, heart, stomach, intestines, bone marrow and skeletal muscles were normal.

Dogs Given 5 Mg. of Di-nitrophenol per Kilogram.—Dog B.—Grossly all the organs were essentially normal.

The results of microscopic examination were as follows: The liver was moderately congested. The lungs showed moderate congestion of the alveolar capillaries. The thyroid gland was normal except that in a few acini the colloid stained bluish with hematoxylin instead of pinkish with eosin. The germinal follicles of the lymph nodes were well developed. One lymph node showed chronic inflammation of mild degree. The islands of Langerhans were rather numerous and normal except for moderate congestion. The spleen was normal, and no pigment was present. The malpighian bodies were of normal size and appearance. In the cortex of the kidneys occasional tiny scars were present and were associated with small collections of round cells. Some of the convoluted tubules showed slight cloudy swelling of the lining epithelium. No casts were observed. The submaxillary salivary glands, testicles, epididymis, heart, suprarenal glands, stomach, intestines, bone marrow, skeletal muscles and prostate were normal.

Dog H.—Grossly all the organs were essentially normal.

The results of microscopic examination were as follows: The liver was moderately congested, and slight fatty infiltration was observed. The lungs were moderately congested throughout. The spleen showed a small amount of brown

granular pigment scattered throughout the pulp. The malpighian bodies were rather prominent and showed slight lymphoid hyperplasia. The cells of the suprarenal cortex were heavily laden with lipoid. The medullary portion of the suprarenals was moderately congested. The kidneys showed spontaneous nephritis of mild degree. A few of the glomeruli showed intraglomerular fibrosis of the tufts with adhesions to Bowman's capsule. These glomeruli were infiltrated by a few round cells. In scattered groups of convoluted tubules there was fatty degeneration of the lining epithelium. In these areas the cells were desquamating and also showed considerable cloudy swelling. The interstitial tissue showed slight fibrous thickening. A few of the tubules contained cellular and hyaline casts. As a whole, however, the renal changes were limited in extent. The bone marrow showed moderate hyperplasia. The endothelial macrophages lining the sinuses were large and contained phagocytosed cellular débris. The testicles, epididymis, heart, thyroid gland, parathyroid glands, lymph nodes and skeletal muscles were normal. This was the animal which showed alterations in the excretion of albumin and cellular infiltrations in the brain. It is likely that all the changes noted were due to a previous attack of distemper and were in no way associated with the administration of di-nitrophenol.

Control Dogs Killed at the End of Six Months (No Di-nitrophenol).—Dog A.—Grossly all the organs were essentially normal.

The results of microscopic examination were as follows: In the liver a few small periportal collections of round cells were present. A few of the hepatic cells possessed foamy cytoplasm and with fat stains showed small areas of fatty degeneration. The lungs showed moderate congestion of the alveolar capillaries. In the spleen there was considerable fibrous thickening of the reticulum as well as of the trabeculae. Moderate amounts of brown granular pigment were deposited in the pulp. The malpighian bodies were normal. The cells of the suprarenal cortex were moderately laden with lipoid. The kidneys showed occasional tiny cortical scars and small groups of round cells. Some of the glomeruli showed slight periglomerular fibrosis. The testicles, epididymis, heart, thyroid gland, parathyroid glands, lymph nodes, bone marrow, stomach, intestines, skeletal muscles, submaxillary salivary glands and prostate were normal.

Dog D.—Grossly all the organs were essentially normal.

The results of microscopic examination were as follows: The liver was moderately congested. Many of the central lobular sinusoids were widely dilated and congested, and there was atrophy of the neighboring liver cells. The lungs were moderately congested throughout. In the pulp of the spleen small amounts of brown granular pigment were present. The cells of the suprarenal cortex were moderately laden with lipoid. In the kidneys a few of the convoluted tubules showed various degrees of fatty degeneration. Dense groups of round cells were present in a few areas. The heart, thyroid gland, lymph nodes, pancreas, bone marrow and stomach were normal.

Dog G.—Grossly all the organs were essentially normal.

The results of microscopic examination were as follows: The liver was moderately congested. The lungs showed moderate congestion of the alveolar capillaries. The islands of Langerhans were rather numerous. The kidneys were moderately congested. The heart, thyroid gland, lymph nodes, spleen, suprarenals, bone marrow, stomach, parathyroid glands, testicles and epididymis were normal.

Comment.—The gross and microscopic studies made did not indicate abnormal changes in the brains of animals acutely and chronically

poisoned by dinitrophenol, at least according to the methods used. There were, moreover, no detectable changes in the other organs and tissues which could be ascribed to the effects of the drug. Therefore, these results were consistent with the negative chemical findings described.

SUMMARY AND CONCLUSIONS

Six dogs receiving di-nitrophenol continuously during a period of six months were observed for possible deleterious effects, as indicated by examinations of the urine, blood and tissues. Three of the animals were given 5 mg. and three 10 mg. of 2, 4, di-nitrophenol per kilogram of body weight daily by mouth. Three dogs without medication were used as controls.

Estimations at intervals of three weeks of the amount of sugar and albumin in the urine and of the hemoglobin and red, white and differential blood cell counts, urea content, icteric index and oxygen capacity of the blood and fragility of the red cells showed no significant or consistent deviations from the normal or control values.

Examinations of the brains of these nine dogs and of three dogs killed with acutely fatal doses of di-nitrophenol showed no demonstrable pathologic changes.

Other organs and tissues of the nine dogs in the series given continuous medication showed no significant pathologic changes grossly or microscopically.

It therefore appears that doses of di-nitrophenol of over three times the usual clinical doses may be given to dogs continuously for at least six months without causing demonstrable injury of vital functions or organs.

Notes and News

Evaluation of Serologic Methods for the Diagnosis of Syphilis.—The Public Health Service, in cooperation with the American Society of Clinical Pathologists, has drafted a plan to evaluate the methods of serologic diagnosis of syphilis in this country.

Support by the Rockefeller Foundation of Medical Sciences.—In the medical sciences the Foundation, during 1933, appropriated $1,173,853. In aid of programs of specific concentration in the fields of psychiatry and public health teaching, appropriations were made to the Johns Hopkins University School of Medicine, Baltimore, for research in psychiatry; to University College, London, for work in biophysics and neurophysiology; to Washington University, St. Louis, for investigations in nerve physiology, and to the Harvard University Medical School, Boston, and the Massachusetts General Hospital for cooperative work in psychiatry. For the development of teaching in public health and preventive medicine an appropriation was made to Dalhousie University, Halifax, Nova Scotia. During 1933 the Foundation provided two hundred and ninety-five fellowships in the medical sciences. In addition, research aid grants in sums varying from $55 to $3,000 enabled sixty-one scientists or groups of scientists to carry on research work.

University News, Promotions, Resignations, Appointments, Deaths, etc.—Frank L. Horsfall, John W. Murray and Albert B. Sabin have been appointed as assistants on the staff of the Rockefeller Institute for Medical Research.

Bailey K. Ashford, Colonel in the Medical Corps of the United States Army and widely known for his pioneer work on hookworm, died on November 1, at the age of 61.

Society News.—The next meeting of the Federation of American Societies for Experimental Biology, in which is included the American Society for Experimental Pathology, will be held in Detroit, April 10 to 13, 1935.

The annual Gross Lecture of the Pathological Society of Philadelphia was given on the evening of December 13 by Dr. Shields Warren, who spoke on "Recent Advances in the Pathology of the Thyroid Gland."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE HEART VALVES AND MUSCLE IN EXPERIMENTAL SCURVY WITH INFECTION. JAMES F. RINEHART and S. R. METTIER, Am. J. Path. **10**:61, 1934.

On the basis of the experimental data reported, and other experimental, epidemiologic and clinical data previously outlined, the theory is advanced that a condition of vitamin C undernutrition may be a necessary background for the development of rheumatic fever; when the insult of infection is combined with the scorbutic state, the pathologic picture of rheumatic fever develops.

THE DEVELOPMENT OF THE PULMONARY SILICOTIC NODULE IN THE EXPERIMENTAL ANIMAL. W. S. LEMON and G. M. HIGGINS, Am. Rev. Tuberc. **28**:470, 1933.

The authors present a new method of introducing suspensions of silica into the lungs of rabbits (using sodium amytal for anesthesia) by means of a tracheal cannula and roentgen localization. With this method they were able to follow the various changes that produce the typical nodule—that build it up, encapsulate and obliterate it, or that disintegrate it, destroy and eliminate it. Such progressive steps cannot be witnessed in the study of silicosis in man. The first and youngest silicotic nodule became recognizable within forty-eight hours. It was a small spherical bit of consolidated parenchyma, lying eccentric to a small bronchus. Within from three to five days strands of fibrous tissue were formed by the fibroblasts in the periphery of the nodule. The lesion became surrounded by them, and they penetrated into the central portions where silica was most abundant. Within seven days the first typical pulmonary silicotic nodules were completed. Within the second week necrosis was well advanced in the central zone, and between the first and sixth months organization was complete. The nodule either became completely fibrotic, or, after first becoming necrotic, showed replacement of the necrosis by mononuclear cells of the histiocytic type which produced argyrophil fibers in vast numbers and obliterated the nodule. Within that same period, however, reactions of degeneration were also observed, in which small or large abscesses had developed. Erosion into the bronchi or the blood vessels or the pleural spaces occurred, and death often resulted from subsequent pneumonia, sepsis or empyema. The foregoing metamorphosis of the typical pulmonary silicotic lesion was completed within six months.

H. J. CORPER.

LEAD IN MULTIPLE SCLEROSIS. W. CONE, C. RUSSEL and R. U. HARWOOD, Arch. Neurol. & Psychiat. **31**:236, 1934.

Lead was found in the urine, spinal fluid and feces in multiple sclerosis. The fact is emphasized that lead may be absorbed early in life and retained by the bones. Under certain conditions (pregnancy, state of acidosis, lactation and diet poor in calcium) it may be liberated, flood the system and produce changes typical of multiple sclerosis.

GEORGE B. HASSIN.

CEREBRAL FAT EMBOLISM. L. S. MERIWETHER and D. C. WILSON, Arch. Neurol. & Psychiat. **31**:338, 1934.

The reaction of microglia in cerebral fat embolism was studied in twenty grown rabbits which received, through the carotid artery, 8 minims (0.48 cc.) of olive oil stained with scarlet red. The animals were kept alive for from two hours to thirty days. The injected fat escaped through the capillary walls and as early as four hours after the injection it was found within the microglial cells. Around

the areas of necrosis the astrocytes became numerous, their processes interlacing with proliferated connective tissue from the neighboring blood vessels and partly with the pial prolongations. An early cerebral change was edema on the side of the injection, but there was no hemorrhage.

GEORGE B. HASSIN.

ETIOLOGY OF AGRANULOCYTIC ANGINA. F. W. MADISON and T. L. SQUIER, J. A. M. A. **102**:755, 1934.

Evidence is presented that agranulocytic angina may depend to some degree on the use of drugs containing amidopyrine and barbiturates.

HEMOGLOBIN INJECTIONS IN RABBITS ANEMIC FROM BLEEDING. D. K. MILLER and C. P. RHOADS, J. Exper. Med. **59**:333, 1934.

An anemia characterized by an increase in the size of the red blood cells and a high color index was produced in rabbits by repeated bleeding and by subcutaneous injection of stroma-free hemoglobin solution. The bone marrow of these rabbits reverted to a more primitive stage than did the marrow of rabbits rendered anemic in the same manner but not treated with hemoglobin.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL HYPERTENSION. H. GOLDBLATT et al., J. Exper. Med. **59**:347, 1934.

These experiments indicate that, in dogs at least, ischemia localized to the kidneys is a sufficient condition for the production of persistently elevated systolic blood pressure. When the constriction of both main renal arteries is made only moderately severe in the beginning, the elevation of systolic blood pressure is unaccompanied by signs of materially decreased renal function. In this respect the hypertension in these animals resembles that which is associated with so-called benign nephrosclerosis in man. Subsequent increase of the constriction of the main renal arteries does not materially damage renal function, probably because of an adequate development of accessory circulation. More delicate methods for detecting a change may yet prove that some damage occurs. Almost complete constriction of both main renal arteries from the beginning results in great elevation of systolic blood pressure, which is accompanied by severe disturbance of renal function and uremia. This resembles the type of hypertension which is associated with so-called malignant nephrosclerosis, in the sense of Fahr. In several of the animals with persistent elevation of systolic blood pressure, anatomic changes were observed in the glomeruli, vessels and parenchyma of the kidneys which are most probably directly referable to the ischemia.

FROM THE AUTHORS' CONCLUSIONS.

EFFECT OF EXTRACT OF THE ANTERIOR PITUITARY ON THE EARLY GROWTH OF THE ALBINO RAT. A. M. TARGOW, J. Exper. Med. **59**:699, 1934.

Castrated male albino rats were given injections of a growth-promoting extract of the anterior lobe of the bovine pituitary gland from the twenty-first day of life (day of castration) to the fifty-sixth day (average for the group), at which time the difference in weight between the treated animals and the controls was first clearly discernible. In comparison with the controls the pituitary-treated animals at this stage showed: (1) a decrease in the weight of the pituitary gland; (2) an increase in the nose-anus length; (3) an increase in the weights of heart, lungs, liver and kidneys, which increase is shown to be of the nature of a splanchnomegaly; (4) an increase in the weight of the blood removed; (5) an increase in the water content of the skin and of the kidneys; (6) a tendency toward an increase in weight of the carcass.

FROM THE AUTHOR'S SUMMARY.

PORPHYRINS IN HUMAN DISEASE. V. R. MASON, CYRIL COURVILLE and E. ZISKIND, Medicine **12**:355, 1933.

Three types of the disease may be recognized: congenital, acute toxic and acute idiopathic hematoporphyria. The congenital type is associated with porphyrinuria, staining of the bones and teeth and striking dermal photosensitivity (hydroa aestivale) appearing usually in the early years of life. The acute type usually appears first after twenty years of life and is characterized by porphyrinuria, acute, painful abdominal symptoms resembling ileus and severe degenerative lesions of the nervous system resembling Landry's paralysis. The majority of patients in this group have used barbituric acid compounds to excess, but in the remainder no causal factor can be discovered. The porphyrins in the urine are coproporphyrin and uroporphyrin. They are probably formed in the hematopoietic organ owing to some fault in the enzymatic synthesis of hemoglobin. The changes in the nervous system consist of extreme degeneration of the motor ganglion cells of the cord and the cerebellar Purkinje cells with slight alteration of the cortical cells. There are also degenerative changes in the posterior ganglion cells and in the abdominal sympathetic ganglion cells. The peripheral nerves show degeneration of both the myelin sheaths and the axis-cylinders. Round cell infiltration was found about the blood vessels and scattered through the neural bundles in the sciatic nerves. Yellow pigment was present in the perivascular spaces of the brain and choroid plexus.

AUTHORS' SUMMARY.

EXPERIMENTAL TOXIC APPROACH TO MENTAL DISEASE. A. FERRARO and J. E. KILMAN, Psychiat. Quart. **7**:115, 1933.

The authors studied the intoxications induced by indol, histamine and potassium cyanide. When cats were given varying amounts of indol subcutaneously, from which all of the animals eventually died, the brain showed varying degrees of degeneration of the cells of the cerebrum, thalamus and hypothalamus as well as slight degenerative changes in the astrocytes and oligodendroglia. Subcutaneous injections of varying amounts of histamine caused slight degenerative changes of the Nissl cells and a central fatty infiltration of the liver, with increase in the lymphoid tissue of the mucosa and submucosa of the intestines. Subcutaneous injections of indol and histamine caused marked lesions in the central nervous system. There were diffuse cerebral lesions, mostly ischemic foci with Nissl degeneration. The neuroglia, astrocytes and oligodendroglia were also degenerated. The liver showed a severe fatty degeneration. In cats given injections of indol and potassium cyanide, the brain changes were similar to but less marked than those caused by indol and histamine combined. It is suggested that small doses of indol, histamine or potassium cyanide may be highly injurious to the central nervous system. The hypothesis is advanced that mental disease may result from a systemic absorption of such poisons from the digestive tract.

WILLIAM FREEMAN.

TRANSPLANTATION OF LIVER. G. R. CAMERON and C. L. OAKLEY, J. Path. & Bact. **38**:17, 1934.

In an autoplastic liver transplant the peripheral cells survive and give rise to new bile ducts and liver cells. Proliferation of the surviving cells commences within two days, each type of cell growing independently and showing no tendency to unite with the other. The liver cells are, however, unstable and soon undergo degeneration and atrophy, with the formation of pigment. The bile ducts persist for long periods unchanged except for dilatation and flattening of their lining cells. Since the grafts are well vascularized it is suggested that the failure of the liver cells to maintain their existence is due to some inherent difference from duct cells in their make-up. Homoioplastic and heteroplastic transplants undergo complete destruction and are eventually absorbed.

AUTHORS' SUMMARY.

EXPERIMENTAL PNEUMOCONIOSIS: INFECTIVE SILICATOSIS. E. H. KETTLE, J. Path. & Bact. **38**:201, 1934.

These experiments form part of a wider investigation which is still in progress, but in themselves they appear to be sufficiently advanced to throw light on two of the fundamental problems in the pathology of pneumonoconiosis, namely, the nature of the dust causing the disease, and the nature of the lesions provoked by it.

Nature of the Dust.—In many industries the working conditions entail the production of dusts, which are suspended in the atmosphere and are harmful to those who inhale them, since they are capable of producing extensive pulmonary fibrosis. In some industries these dusts are relatively simple in their composition; in others they consist of a variety of substances; but in all the occupations in which there is a recognizable dust hazard a considerable proportion of the suspended particles consists of some form of silicon. In fact, according to modern views, pneumonoconiosis and silicosis are practically synonymous terms. It is not generally accepted, however, that all forms of silicon are productive of silicosis. The oxide, silica, is universally acknowledged to be dangerous; but with the single exception of asbestos, a complex silicate of iron and magnesium, it is commonly held that silicates are innocuous. Since there is general agreement that quartz and other varieties of crystalline silica are not harmful when inhaled into the lung, merely because of their physical state, there seems little reason why other compounds of silicon should not also possess the power of producing pulmonary fibrosis, and, indeed, W. R. Jones in 1933 brought forward a strong case in support of the view that sericite, a potassium aluminum silicate, is the cause of much of the industrial silicosis. For some time I have been working with an allied silicate, kaolin, and have shown that it possesses the characteristics of a potentially dangerous dust. The present experiments show that kaolin is capable under certain conditions of causing extensive lesions when introduced into the lungs of guinea-pigs and is, indeed, one of the most active dusts with which I have worked.

Nature of the Lesions.—It is generally acknowledged that even a serious degree of pulmonary fibrosis may be caused by the inhalation of silica without any accessory factor, but this pure or simple silicosis is rarely of clinical significance; nearly always silicosis is associated with tuberculosis, and my experience with silicosis in this country leads me to place increasing importance on the infective factor. I rarely see a case of simple silicosis, and even in those cases in which tuberculosis appeared to have been definitely grafted on to a silicotic lung, there has often seemed to me to be strong evidence that the apparently pneumonoconiotic lesions were infective from the beginning. These experiments support this view, for they show that lesions can be rapidly produced in the lungs of guinea-pigs when a dust is combined with an infective process, whereas lesions can be produced only with the greatest difficulty, if at all, by the dust alone.

FROM THE AUTHOR'S CONCLUSIONS.

THE MANIFOLD EFFECTS OF CASTRATION IN MALE RATS. V. KORENCHEVSKY and M. DENNISON, J. Path. & Bact. **38**:231, 1934.

Castration in male rats produces the following definite changes: striking atrophy of the sex organs (prostate, seminal vesicles and penis), slight atrophy of the thyroid gland and, about seventy days after castration, of the liver and kidneys; delay in involution of the thymus and hypertrophy of the suprarenal glands and hypophysis. In addition most animals show an increase in the deposition of fat and a decrease in body weight or in gain of body weight of small and varying degree. It is possible that the very slight decrease in the weight of the heart, which, on the average, was observed in most castrated rats as compared with their normal litter mates may also be specific. These changes are produced by changes in the tissues of the organs and not by changes in the blood content.

FROM THE AUTHORS' SUMMARY.

FAT MOBILIZATION IN STARVATION. J. HENRY DIBLE and J. LIBMAN, J. Path. & Bact. **39**:269, 1934.

Our earlier finding that in the rat the extent of the fat infiltration in the liver in starvation is determined by the quantity of fat available in the animal's storage depots has been confirmed in rabbits starved for periods up to seven days and losing as much as 27 per cent of body weight. An increased percentage of fat in the liver cell is a constant result of starvation, but in animals whose stored fat is meager the increase may be only a relative one, since in these animals the shrinkage of the liver in starvation is early and marked. On the other hand where a sufficient supply of mobilizable fat is available there is an absolute increase in hepatic fat. In very adipose individuals in the earlier stages of starvation this may more than counterbalance any loss in the weight of the liver.

FROM THE AUTHORS' SUMMARY.

XEROPHTHALMIA, TRIGEMINAL DEGENERATION AND VITAMIN A DEFICIENCY. E. MELLANBY, J. Path. & Bact. **38**:391, 1934.

Evidence is given which suggests that xerophthalmia produced in animals by diets deficient in vitamin A and carotene may be secondary to a loss of the neurotrophic control normally exerted on the cornea by the ophthalmic division of the trigeminal nerve. When xerophthalmia is present, the corresponding trigeminal nerve usually shows degenerative changes in the myelin sheaths, and in the rabbit their development is commonly almost synchronous. In early and slight xerophthalmia when the corneal epithelium becomes normal as the result of adding carotene or vitamin A to the diet, the nerve also becomes normal. In such cases the myelin degeneration is of the annular type, and although the fibers may be swollen the myelin does not invade the axis-cylinder. This type of nerve degeneration seems capable of rapid recovery. In more severe cases of xerophthalmia, in addition to degeneration of the annular type, many of the fibers show typical wallerian degeneration, the axis-cylinder being invaded by degenerated myelin, while globules of the latter are scattered throughout the nerve. In cases of this type recovery of the nerve fiber either does not take place or does so only after months of vitamin A or carotene therapy. The nerve cells of the gasserian ganglion as well as their nerve fibers show degenerative changes. Indeed it is possible that the original lesion is in the cells, and that the trigeminal changes, peripheral and central, are secondary thereto. In the rat, in which as the result of vitamin A deficiency the eyelids become puffy, the cornea may escape xerophthalmic changes. In such cases also the trigeminal nerve shows demyelinization. Since degeneration of the afferent nerves is widespread in animals brought up under these experimental conditions, it is probable that hyperplasia and metaplasia of other epithelial and mucosal surfaces throughout the body, and the subsequent invasion of these tissues by micro-organisms, are also related to changes in their afferent nerve supply.

FROM THE AUTHOR'S SUMMARY.

OEDEMA IN EXPERIMENTAL NEPHRITIS. J. S. DUNN, E. G. OASTLER and S. L. THOMPSETT, J. Path. & Bact. **38**:421, 1934.

Extensive subcutaneous edema and serous transudates can be obtained in nephritis produced by mercuric chloride and potassium dichromate as well as by uranium, provided the renal lesions are severe enough and the animals ingest sufficient fluid. The greater liability to edema in uranium nephritis is probably due to the severe damage to renal structure and function which uranium causes, combined with low general toxicity and noninterference with nutrition. The essential cause of the edema in experimental tubular nephritis is failure of the kidney to excrete sufficient fluid. Oliguria is due to failure of the damaged renal tubules as conducting channels.

FROM THE AUTHORS' CONCLUSIONS.

RESEARCH ON BURNS. S. NICOLAU and P. POINCLOUX, Ann. Inst. Pasteur **52**: 217, 1934.

"In the blood of burned animals (rabbits, man) there develops a special leukocytic reaction characterized by: (*a*) multiplication of large mononuclears; (*b*) development of young primordial cells; (*c*) appearance of the cells of Rieder, and (*d*) slight increase in Türk cells. This reaction, which we call 'megamononucleosis,' is precocious, intense, lasting; it is proportional to the intensity and to the extent of the burns; it is interpreted, we believe, as a defense of the organism of the burned against the intoxication to which it is submitted. That those burned are submitted to an intoxication may be shown by intra-abdominal injection of their blood into a mouse (from 0.5 to 2 cc.), which often kills these animals. The principle toxic for mice is more abundant in the whole blood than in the serum; it exists in the liver in sufficient quantity to be demonstrated. Blood of those burned, or that of an animal which has succumbed to the injection of such blood, induces flocculation of ordinary meat broth. Anesthesia exerts a definite protective action against the risk of rapid death to which animals exposed to heat are subject."

AUTHORS' CONCLUSIONS.

EXPERIMENTAL INTESTINAL OBSTRUCTION. J. BOTTIN, Arch. internat. de. méd. expér. **9**:51, 1934.

In dogs subjected to intestinal obstruction at a point 5 or 6 cm. below the mouth of the main duct of the pancreas, a concentration of blood elements with a relative diminution in blood volume developed, with a progressive fall in arterial blood pressure. Bottin concludes that the syndrome in high intestinal obstruction is due largely to dehydration.

RALPH FULLER.

FORMATION OF BONE AND CARTILAGE AFTER INJECTIONS OF QUININE HYDROCHLORIDE. R. SEVERI, Pathologica **25**:611, 1933.

Rabbits were given intramuscular injections of a solution of quinine hydrochloride. Formation of bone in the muscle resulted in two animals, and of cartilage in three animals. Experiments on dogs and white mice failed because the salt is toxic for these animals.

E. VON HAAM.

NORMAL AND PATHOLOGIC HISTOPHYSIOLOGY OF THE HUMAN THYROID EPITHELIUM. JOHANNES WAHLBERG, Arb. a. d. path. Inst. Univ. Helsingfors **7**:197, 1933.

In the normal thyroid the greater part of the parenchyma is inactive and serves as a functional reserve. Colloid is stored in most of the follicles. This occurs through a process of secretion in the cytoplasm in the form of vacuoles, which are emptied into the follicular cavity. In a certain number of follicles, the hormone follicles, there is a reversal of the process of secretion from the apical to the basal portion of the cell, where large vacuoles are formed which empty directly into the capillaries or the intercellular spaces and lymphatics. In colloid goiter the apical direction of secretion is pathologically increased but is qualitatively similar to the normal process. In thyrotoxicosis the histophysiology indicates that there is an excessive secretion of thyroid hormone. In cases of goiter without clinical signs of toxicosis in which mechanical pressure is relieved by surgical means, with subsequent relief of nervous and circulatory symptoms not due to pressure, microscopic examination shows definite evidence of thyrotoxicosis. The clinical improvement after preoperative treatment with iodine in thyrotoxicosis corresponds to the histophysiologic reversal of polarity in secretion from basal to apical type with storage of colloid in the follicles.

JACOB KLEIN.

ARTIFICIAL ENDOMETRIOSIS. H. H. SCHMID, Arch. f. Gynäk. **155**:217, 1933.

Since 1929 Schmid has practiced vaginal transplantation of uterine mucosa where hysterectomy had to be done. The purpose was to encourage menstruation for its psychic and physical benefits. The procedure, which is quite simple and harmless, consists in the insertion of some uterine mucosa between the posterior vaginal wall and the peritoneum. Thus far there have been nineteen cases in which such transplantation was successful. The autotransplants healed and maintained normal menstrual function.

JACOB KLEIN.

Pathologic Anatomy

SWELLING OF THE MICROGLIA: REACTION TO INTOXICATION. ELI MARCOVITZ AND BERNARD J. ALPERS, Arch. Neurol. & Psychiat. **31**:1045, 1934.

While the behavior of the microglia in destructive lesions of the central nervous system has been well studied, its behavior in toxic conditions is much less well understood. From experiments and studies on human material Marcovitz and Alpers have come to the conclusion that microglia shows definite changes in acute and chronic states. They injected intravenously and in one case subdurally phosphorated oil (N. F.) two or three times a week into seventeen male rabbits, and killed them at intervals of from a few days to several weeks later. The changes in acute cases were loss of spines and side branches and swelling of the process, nucleus and cytoplasm. Later the processes became thicker and broke up into smaller fragments, and the cell body became vacuolated. In subacute and chronic cases (many weeks' duration) the cells including the spines became hypertrophied but finally exhibited varicosities and vacuolation of the branches. No lipoids were found in them, nor were ganglion cell changes present. The authors found similar changes in human brains in Alzheimer's disease, poliomyelitis, meningitis and meningo-encephalitis. The lesion is mainly regressive, although it possesses some reparative features.

GEORGE B. HASSIN.

HISTOLOGY OF THE CENTRAL NERVOUS SYSTEM IN THE ST. LOUIS EPIDEMIC OF ENCEPHALITIS. ARTHUR WEIL, Arch. Neurol. & Psychiat. **31**:1139, 1934.

As epidemic encephalitis may present a great variety of clinical pictures it does not seem reasonable to consider the slight variations presented by the St. Louis epidemic (occurrence in the summer months, absence of oculomotor nerve paralysis, restlessness preceding somnolence) as signs of a new type of encephalitis. Nor have the histologic changes differed from those seen in the classic type, as shown by the observations of Weil on eight brains from patients who died during the 1933 epidemic of encephalitis in St. Louis. He found a mild leptomeningitis, especially marked at the base of the brain; perivascular infiltrations of the veins and arteries, mainly by lymphocytes; formation of glia nodules in the white substance, in which oligodendroglia predominated; absence of hemorrhages; mild ganglion cell changes, and a predominance of inflammatory changes in the thalamencephalon and midbrain. In two cases, similar inflammatory phenomena were also present in the spinal cord. Micro-organisms (in the form of diplococci, short chains of cocci or small agglutinated colonies) were found in the subarachnoid space or within the walls of smaller blood vessels and occasionally within foci of inflammatory reaction.

GEORGE B. HASSIN.

ENCEPHALOMALACIA IN INFANTS. I. B. DIAMOND, Arch. Neurol. & Psychiat. **31**: 1153, 1934.

Cerebral changes in infants described by Virchow as interstitial encephalitis have been studied by Diamond in two infants, aged 7 weeks and 3½ months, respectively. He found marked degenerative changes with formation of lacunae, vast accumulations of fat granule bodies, proliferation of blood vessels, reduction

in size of the affected hemisphere, reactive glial phenomena and so-called aseptic meningitis (accumulation in the subarachnoid space of proliferated fibroblasts, mesothelial cells, polyblasts, lymphocytes and gitter cells). The changes were considered by Virchow to be inflammatory and a manifestation of fatty metamorphosis of the glia, while later observers held trauma to be the most common, if not the only, cause. In Diamond's cases the cause of the changes justly classified as degenerative was in one case a marked infectious process which started in an eye and necessitated its enucleation, and, in the second case, a severe intoxication.

GEORGE B. HASSIN.

SCLEROTIC ATROPHY OF THE CEREBELLUM. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **31**:1205, 1934.

In two cases of sclerotic atrophy of the cerebellum, a condition known under many other names (e. g., "primary parenchymatous atrophy" or "late cerebellar cortical atrophy"), there was practically a complete destruction of the ganglion cells of the molecular, Purkinje cell and granular layers with secondary involvement of the white substance including the mossy and climbing fibers. The destroyed parenchyma was replaced by a feltwork of glial fibers and a row of so-called Bergmann's glia nuclei. In exceptionally rare instances, Purkinje cells could be discerned, but they were calcified and misplaced. The degeneration was in patches and was confined to a few leaflets of the semilunar and a part of the quadrilateral lobe. As the patches resulted from primary destruction of the gray matter (the ganglion cells) and secondary involvement of the white substance, they differed from those of multiple sclerosis, in which not the ganglion cells but the white matter is primarily destroyed. In spite of such a far-gone cerebellar lesion clinical cerebellar signs were not in evidence. The clinical picture in one case was leukemia; in the other, dementia praecox.

AUTHOR'S ABSTRACT.

BIPOLAR SPONGIOBLASTOMA IN THE REGION OF THE HYPOTHALAMUS, ASSOCIATED WITH INFANTILISM AND WITHOUT DWARFISM. WALLACE B. HAMBY, Arch. Neurol. & Psychiat. **31**:1258, 1934.

Infantilism caused not by a pituitary lesion but by a glioma of the hypothalamic region was observed by Hamby in a man aged 22, who six months prior to examination began to suffer from headaches, vomiting and later from rapidly failing vision. For two years there were polydipsia and polyuria. The patient was of large size, his sexual organs and distribution of fat were infantile, and there was lack of axillary hair. There was a marked bilateral papilledema with a binasal hemianopia, and the roentgen examination revealed unfused epiphyses at the lower ends of the radii and ulnae and the bones of the hands and a calcified supracellular tumor. At necropsy the tumor proved to be a bipolar spongioblastoma. It was located above the hypophysis, almost filled the entire third ventricle and consisted of spindle-shaped cells, rich in cytoplasm, which "streamed away from the nucleus in two long processes" and contained a fairly large nucleus. Some cells were multinucleated.

GEORGE B. HASSIN.

A CONSTITUTIONAL ABNORMALITY OF THE POLYMORPH LEUCOCYTES. A. F. B. SHAW, J. Path. & Bact. **38**:259, 1934.

A case is described of a persistent deflection of the polymorphonuclear count to the left associated with an abnormally complex nuclear configuration of all the class I cells. There is no nuclear change in the other leukocytes, and the total and differential counts are normal. It is claimed that the condition is a constitutional abnormality of the polymorphonuclear leukocytes. Hereditary transmission was not found, but the evidence is incomplete. No record of a similar case has been found in the literature, and the condition differs in certain important respects from "Pelger's familial anomaly of nuclei."

FROM THE AUTHOR'S SUMMARY.

INFLAMMATION IN THE CATERPILLARS OF LEPIDOPTERA. G. R. CAMERON, J. Path. & Bact. **38**:441, 1934.

Caterpillars possess an effective phagocytic mechanism composed of (1) the blood cells, of which there are three main types: (*a*) lymphocytes, (*b*) leukocytes and (*c*) spherule cells; (2) the pericardial cells; (3) certain cells in the fat body.

DISSECTING ANEURYSMS. T. SHENNAN, Medical Research Council, Spec. Rep. Ser. no. 193, 1934.

This report gives an analysis of 273 cases of dissecting aneurysm described in the literature and 17 cases studied by the author himself. It concerns chiefly dissecting aneurysms of the aorta. The feature common to all the cases is degeneration in the media, which usually gives way before the intima ruptures. This degeneration usually arises "as a result of toxic insults of varying character sustained during life." Syphilis does not play a prominent part in the genesis of dissecting aneurysm. Proximity of the primary tear to the heart appears to favor slightly the extent of the dissection and to shorten the period of survival. The dissection distal to the primary rupture is usually more important and more extensive than that proximal to the rupture. Shennan regards the predominance of primary ruptures in the ascending aorta as explainable by the abrupt diastolic recoil meeting the resistance of the closed aortic valve. The distal reentrance of the dissecting blood into the lumen, which allows free circulation through the new channel is "the most important determining factor in the healing process."

FROM THE AUTHOR'S SUMMARY.

HISTOLOGIC LESIONS IN EXPERIMENTAL PNEUMONIC PLAGUE. J. BABLET and G. GIRARD, Ann. Inst. Pasteur **52**:155, 1934.

Guinea-pigs were intratracheally inoculated. Alveolar foci with invasion of the pulmonary lymphatic system were established and multiplied within forty-eight hours, without breaking into the blood capillaries. Experimental pneumonic plague was thus definitely established. The evolution of the infection was histologically similar to that of human plague.

FROM THE AUTHORS' CONCLUSIONS.

THE ENDOCRINE GLANDS IN CIRRHOSIS OF THE LIVER. C. FITTIPALDI, Pathologica **25**:248, 1933.

In an anatomic study of the endocrine glands in the course of cirrhosis of the liver, Fittipaldi found that the parathyroid and pineal glands showed histologic changes in only a few cases. In the hypophysis and the suprarenal glands very slight changes were noted. The thyroid gland, pancreas and testicles, however, showed degenerative changes in every case. In most of these cases the changes may be considered as senile or arteriosclerotic processes. He believes, therefore, that there is no correlation between the endocrine glands and the cirrhotic process, except that the changes in the glands may be considered to be an expression of an abnormal condition, in the sense of an imbalance of the mesenchyma.

E. VON HAAM.

FATTY INFARCT OF THE LIVER. S. MARRAS, Pathologica **25**:798, 1933.

Two cases of fatty infarct of the liver (Cesaris Demel, A.: *Pathologica* **24**:532, 1932) are described. The condition is a fatty degeneration in the form of a sharply limited infarct-like focus, easily recognized by its yellow color and present without diffuse degeneration. It arises from a circumscribed degeneration of small branches of the hepatic artery with deficient oxygenation of the corresponding hepatic tissue.

E. VON HAAM.

NATURE AND ORIGIN OF HYALINE THROMBI OF THE CEREBRAL VESSELS. M. MANDELSTAMM, Beitr. z. path. Anat. u. z. allg. Path. **92**:476, 1934.

A series of more than a hundred brains were examined microscopically. Hyaline thrombi were observed in the cerebral capillaries and postcapillaries somewhat more frequently in cases of infection and in certain psychoses, but bore no very definite relation to the general condition before death. The thrombi are not composed of fibrin or cellular derivatives, but consist of a lipoid protein combination that is coagulated out of the blood plasma during a state of capillary stasis during which water is withdrawn from the vessels into the surrounding brain tissue. The globular or beaded shape of the masses is brought about by capillary contraction acting on the viscid coagulum.

O. T. SCHULTZ.

ERYTHROLEUKOBLASTOSIS, ICTERUS GRAVIS AND CONGENITAL ANASARCA. R. PETERS, Beitr. z. path. Anat. u. z. allg. Path. **92**:531, 1934.

Peters presents a study of a case of icterus gravis and one of congenital anasarca in children of the same mother. The infant with anasarca, a boy who died immediately after birth, was born two and one-half years after the infant, a girl, who died on the third day after birth of icterus gravis. Two previous children were normal, as were both parents. Common to both the children who died was marked erythroleukoblastosis in the liver, spleen and kidneys. The author tabulates and discusses seventy-five cases of congenital anasarca and fifty-two of icterus gravis in which there was microscopic examination. With Schridde, von Gierke and others, he considers both conditions to be manifestations of the same congenital maldevelopment, the outstanding characteristic of which is erythroleukoblastosis. Icterus gravis is frequently associated with ascites, and congenital anasarca with jaundice. Congenital anasarca is held to be the more severe grade of the process. The infants are usually born prematurely and are dead at birth or die shortly thereafter. In icterus gravis the duration of pregnancy is longer and may be normal; the child lives for a few days, and some probably recover.

O. T. SCHULTZ.

SIZE AND NUCLEAR, LEUKOCYTIC AND FAT CONTENT OF THE RENAL GLOMERULUS. O. SOMMER, Beitr. z. path. Anat. u. z. allg. Path. **92**:567, 1934.

In the kidneys obtained at 100 consecutive, unselected necropsies embracing all age periods up to the eighty-first year, the absolute weight, the weight in relation to body weight, the size of the glomeruli, and their nuclear, leukocytic and lipoid contents were determined. The size was determined by measuring the maximum and minimum diameters of 30 glomeruli in each kidney; the nuclei were counted in an equal number. The object of the investigation was to establish norms for various age periods. The weight of the kidney increases progressively and rapidly from 25 Gm. at birth to 260 Gm. at 20 years, remaining fairly unknown during the rest of life. The weight of the kidney relative to body weight undergoes a marked and rapid increase immediately after birth, ascribed to the rapid development of glomeruli and their taking on of function at birth; the relative weight then drops rapidly, to maintain a fairly even level throughout life. The average diameter of the glomeruli increases from 80 microns at birth to 175 microns at 30 years and remains fairly uniform until 60 years, when a slight progressive decrease occurs. The number of glomerular nuclei increases from 120 at birth to 155 at 35 years, beyond which period there is a slight decrease. The average number of oxidase-positive leukocytes increases from 4 at birth to 8 at 20 years and then remains fairly uniform; the number appears to depend on the blood content of the glomerulus. Stainable lipoid in the capsular epithelium increases rapidly from the fifteenth to the thirteenth year and then more slowly. The material is held to be a wear-and-tear pigment.

O. T. SCHULTZ.

BILATERAL RENAL APLASIA. H. MADESSON, Centralbl. f. allg. Path. u. path. Anat. **60**:1, 1934.

Following a review of the embryology of the kidney are detailed reports of necropsies on four new-born children in whose bodies no kidneys were found. All four of these children were males weighing from 1,500 to 3,200 Gm. who were born after long labors, up to sixty-six hours. In three bodies there were no kidneys, ureters or renal arteries; in one the left ureter coursed from a fibrous nodule in the region of the left suprarenal gland to an uncertain termination in the pelvis of the body. In the latter there was no urinary bladder, and only a lumenless fold of skin was present at the normal site of the penis. A penis, patent distally for from 5 to 15 mm., was present on each of the other three bodies. Two of these babies were born of the same parents, a normal sister being born in the interval between the two boys. The children exhibiting these marked anomalies lived from twenty to sixty minutes and apparently died of asphyxia. The author reviews the theories of the causation of renal aplasia and believes that the conditions which he encountered can best be explained on a chromosome deficiency basis.

GEORGE RUKSTINAT.

MYOCARDIAL CHANGES IN EPILEPSY AND THEIR RELATIONS TO ANGINA PECTORIS. K. NEUBÜRGER, Frankfurt. Ztschr. f. Path. **46**:14, 1933.

Gruber and Lanz reported changes in the myocardium in epilepsy. Neubürger examined the hearts of thirty-four patients who suffered from epilepsy and who died before reaching the age of 40. In fourteen he found myocardial changes characterized by simple degenerations of the myocardial fibers, progressive necrosis and scars. The changes were more common in the left ventricle, particularly in the cranial portions of the papillary muscles. An interference with the nutrition of the myocardium from spasm of the smaller vessels is held responsible. It is also possible that tonic contractions of the heart over a long period of time may have led to a mechanical compression of small branches of the coronary arteries, resulting in vascular disturbances. The author believes that coincidental with every severe epileptic attack there may also be an attack of angina pectoris. The latter might escape clinical observation because of the severity of the epileptic fit. Death occurring during the epileptic attack in some instances is the result of the myocardial changes which, however, may be difficult to demonstrate histologically.

O. SAPHIR.

CONGENITAL ADENOMYOSIS. R. WEYENETH, Frankfurt. Ztschr. f. Path. **46**:43, 1933.

In forty-two girls aged up to 14 years four instances of endometrial structures within the myometrium were found. Various other congenital anomalies were present also, including a case of true hermaphrodism, which is described in detail. The author also describes a case of uterus didelphys with endometrial structures throughout the entire left half. Adenomyosis of the uterus and of the tube should be regarded as malformations resulting from extension of the endometrium into the myometrium during the fetal period or from cutting off of epithelial elements of the müllerian duct.

O. SAPHIR.

THE PARATHYROID GLANDS IN DISEASES OF THE KIDNEYS. P. RADNAI, Frankfurt. Ztschr. f. Path. **46**:97, 1933.

There is disturbance in the calcium metabolism in chronic nephritis and nephrosclerosis, and recently changes have been described in the parathyroid glands in disturbed calcium metabolism. For these reasons Radnai examined the parathyroids in primary renal disease. He concludes that there are relatively more acidophilic cells in these glands in renal disease than otherwise.

O. SAPHIR.

THE NATURE AND HISTOGENESIS OF SO-CALLED BASAL CELL CARCINOMA. M. GLASUNOW, Frankfurt. Ztschr. f. Path. **46**:140, 1933.

Basal cell carcinoma is characterized by slow course, superficially destructive growth, absence of metastasis and cachexia, and marked sensitivity to chemical and physical factors. Only ectodermal regions are involved. In most cases the tumor occurs in the skin of the face. Up to date it has not been possible to produce this type of tumor experimentally. Because of the various histologic forms of the tumor it seems likely that it arises from a primary multipotent cell of embryonal character. On the face the tumor often arises in the region of the point of union of the facial clefts.

O. SAPHIR.

SEVERE NECROSIS OF THE COLON FROM CONTUSION OF THE ABDOMEN. F. WAGNER, Frankfurt. Ztschr. f. Path. **46**:185, 1933.

A 50 year old man suffered a severe trauma of the abdomen. Four days later severe abdominal pains set in with fever. The patient died two days after operation. At autopsy intestinal perforation could not be found. In many places the muscularis of the colon was torn, and here the mucosa and submucosa projected into the peritoneal cavity. The tears in the muscularis were the direct result of the trauma. Formation of thrombi within the vessels of the intestines secondarily led to the necrosis of the mucosa and submucosa.

O. SAPHIR.

CHANGES IN THE LIVER IN THYROTOXICOSIS. R. RÖSSLE, Virchows Arch. f. path. Anat. **291**:1, 1933.

A double number of *Virchows Archiv*, comprising 570 pages, consists of contributions from Rössle's institute in Berlin. In the opening article Rössle describes and discusses changes in the liver in thyrotoxicosis which he has seen repeatedly in the course of the past twenty years but which have received little attention in the literature. The gross alterations are slight; interlobular fibrosis of the subcapsular zone is sometimes evident to the naked eye. The histologic changes in selected cases are described as illustrative of the five groups into which Rössle divided his material: cases with old changes; cases with slight and slowly developing alterations; cases with recurrent changes; cases with acute alterations, and those with an unusual course ending in cirrhosis. The acute alterations consist in necroses in the central zone or about the central vein of the lobules; the process may be so marked as to simulate acute or subacute yellow atrophy. Associated with the necroses are focal changes in the capillary endothelium leading to altered distribution of the blood and to serous exudation, which leads Rössle to use the term "serous hepatitis." In later stages sclerosis of the parenchyma occurs, especially in the subcapsular zone; this process may be associated with true cirrhosis. No single alteration is characteristic of thyrotoxicosis, but the series of changes is characteristic and is due to the thyrotoxicosis. The sclerosis is due to fibrils that are formed independently of fibril-forming cells, that is, fibroblasts and capillary endothelium. The fibrils are formed by physicochemical action in the serous exudate as in a culture medium. Rössle believes that such acellular fibril formation may be an important factor in the sclerosis of other organs.

O. T. SCHULTZ.

MALIGNANT NEPHROSCLEROSIS. P. SCHÜRMANN AND H. E. MACMAHON, Virchows Arch. f. path. Anat. **291**:47, 1933.

In a profusely illustrated monograph of 172 pages, the authors discuss the clinical symptomatology and the gross and microscopic pathology of malignant nephrosclerosis based on a very full and detailed description of thirty-seven cases. This is followed by a section devoted to the differential diagnosis of malignant nephrosclerosis from the benign form, and from glomerulonephritis, periarteritis nodosa and other cardiovascular-renal diseases. In a final section they discuss the

pathogenesis and nature of the essential vascular lesion of malignant nephrosclerosis. This lesion is arteriolonecrosis, in contrast to the arteriosclerosis of benign nephrosclerosis. The necrosis is the result of degeneration or injury of the endothelium and its basement membrane. The endothelium is looked on as a barrier that normally protects the blood and the subendothelial tissues of the arteriole and of the organ from each other. When this barrier is broken the blood acts harmfully on the subendothelial tissues, causing hyperplasia, histolysis or necrosis, depending on the degree of action. The tissues and tissue fluids in turn act harmfully on the blood, causing precipitation of fibrin. In the arterioles and renal glomerular vessels the precipitation of fibrin leads to thrombosis and necrosis. For this process of destruction of the blood-tissue barrier the word "dysoria" has been coined, the root of the word coming from the Greek word meaning barrier. Two forms of malignant nephrosclerosis are recognized. One begins with arterial hypertension, which may be the result of a variety of factors, and leads to dysoria and the full-blown picture of malignant nephrosclerosis; this is the genuine form of Volhard. The other form begins acutely as a primary renal disease resulting from exogenous toxic factors and proceeding to the characteristic vascular lesion; this is the exogenous toxic form of Fahr.

O. T. SCHULTZ.

ATYPICAL AMYLOIDOSIS. A. STRAUSS, Virchows Arch. f. path. Anat. **291**:218, 1933.

The literature contains records of a gradually increasing number of examples of amyloidosis that differ from the usual, typical form in the absence of involvement of the organs characteristically involved in true amyloidosis, in a predominant involvement of the walls of the smaller muscular arteries and of striped muscle and adipose tissue, in the absence of an underlying condition like suppuration to which the condition may be due, and in the atypical character of the microchemical reactions. For this atypical form of amyloidosis the name "paramyloidosis" is proposed. The condition reported by Strauss occurred in a man aged 72. Deposition of material morphologically like amyloid but not giving all the characteristic reactions of this substance had increased the thickness of the walls of smaller arteries up to ten times the normal. On the epicardium and pericardium was a layer of similar material from 1 to 2 cm. thick. It was present widely in adipose tissue. Necrosis and chronic suppuration were absent. Strauss briefly discusses twenty-eight previously reported cases of atypical amyloidosis. Common to all was the rather advanced age of the persons with paramyloidosis.

O. T. SCHULTZ.

MEASUREMENT OF THE CONSISTENCY OF THE BRAIN. R. NEUMANN, Virchows Arch. f. path. Anat. **291**:341, 1933.

The sclerometer and Brinell methods of determining consistency were found to be not applicable to the brain because of the semifluid character of this organ. Neumann devised and fully describes an apparatus that measures consistency by the depth to which a cone of definite weight, size and shape penetrates the tissue by its own weight in the space of five seconds. The results are recorded in the form of an enlarged graph on a revolving kymograph drum. Differences in penetration of 0.1 mm. are accurately recorded. The mathematical analysis of the graphs, which looks very complicated to an old-fashioned pathologist, is described in detail. With this apparatus the consistency of 100 brains, removed as soon after death as possible, was determined, 100 to 200 determinations being made on each brain. The cerebrum was cut into a series of frontal sections, the pons and medulla into transverse sections, and the lateral lobes of the cerebellum into sagittal sections. On these tissue slabs the consistency of the various white and gray areas was determined. The consistency increased during the first thirty to forty hours after death and then decreased. Changes in consistency resulting from

a variety of factors affected chiefly the white matter. The consistency of hyperemic brains was higher than that of anemic brains. The consistency of edematous brains varied from high to low. Swelling of the brain, especially in the presence of acute infection, was associated with diminished consistency. The consistency of atrophic brains was increased. There was no correlation between consistency of the brain and sex, age and habitus. In diabetes mellitus the brain had an unusually high consistency, described as a peculiar density different from that of the sclerotic brain, which could not be accounted for by histologic alterations. In disturbed fat metabolism the consistency was also increased. The brain in a case of systemic paramyloidosis had a high consistency, although microscopic examination did not reveal the presence of amyloid.

O. T. SCHULTZ.

DETERMINATION OF THE MUSCLE MASS OF THE STOMACH. K. HELMKE, Virchows Arch. f. path. Anat. **291**:507, 1933.

One hundred and forty-four human stomachs were used in the study here reported. The stomach was opened, laid flat, and its surface area determined by measurement. All external extraneous tissue was removed down to the peritoneum. The mucosa and submucosa were removed together from the fibromuscular coats. The weight of the muscle mass and that of the mucosa and submucosa were determined in the fresh, moist state and after drying to constant weight. The fat contents of the two portions were determined. The average weight of the muscle mass of the normal stomach was 0.87 Gm. per kilogram of body weight; that of the mucosa and submucosa was 1.2 Gm. The maximum weight of the muscle mass was 3.1 Gm. per kilogram of body weight, in a man with pyloric stenosis due to ulcer. The minimum weight was 0.57 Gm., in a man with pulmonary tuberculosis. The weight of the muscle was increased in pyloric obstruction, diabetes mellitus and hepatic cirrhosis. The mucosa and submucosa made up 58 per cent of the total weight of the stomach. This proportion was decreased in achylia, pernicious anemia, old age and chronic gastritis. It was increased in plethora and in some cases of chronic gastric catarrh. The water content of the wall of the stomach was increased in uremic gastritis, passive congestion, ascites, cirrhosis of the liver and sepsis. The fat content of the wall paralleled that of the body. The mucosa of the diabetic stomach contained exceptionally large amounts of fat. The average surface area of the normal stomach was 473 sq. cm. The maximum observed was 792 sq. cm., in the stomach with the highest muscle weight. Small fibromyomas at the cardia were seen in 10 per cent of the stomachs examined.

O. T. SCHULTZ.

HYPERTROPHY OF THE GUMS. F. GERLING, Virchows Arch. f. path. Anat. **291**: 522, 1933.

Gerling presents two cases of hypertrophy of the gums. In the first, that of a girl who died at the age of 10 years, the condition had been present since the fifth year of life. Previous to this time the child had had encephalitis followed by hemiplegia. In psychoses in which the mouth is held open, hypertrophy of the gums has been noted. The child began to menstruate at 7 years of age and exhibited other evidences of precocious puberty, supposedly the result of endocrine disturbance. In previously reported cases gingival hypertrophy has been ascribed to endocrine dysfunction. Gerling thinks that both factors may have played a part in this case. The enlargement of the gums was due to diffuse increase in collagenous connective tissue, which did not appear to be inflammatory in origin. The differentiation of this condition from hyperplastic gingivitis is discussed. The second case was one of acute myeloblastic leukemia. The gingival hypertrophy was due to myeloblastic infiltration of the tissues of the gums.

O. T. SCHULTZ.

A Case of Cleidocranial Dysostosis. P. Ladewig, Virchows Arch. f. path. Anat. **291**:542, 1933.

The rare condition that P. Marie and Sainton described in 1898 under the name "dysostosis cleidocranialis hereditaria" is characterized by small body stature; by maldevelopment of the cranial vault with prominence of the frontal and parietal regions; by late or deficient ossification of sutures and fontanels, which are closed by multiple irregular masses and nodules of bone; by an abnormally small face; by deformity of the jaws with many unerupted teeth, and by bilateral partial or complete absence of the clavicles. There may be other skeletal deformities. Anatomic descriptions are meager. This Ladewig ascribes to the fact that the persons with the deformities are usually well psychically and as regards their general health; the condition goes unrecognized and escapes the pathologist. In the case described by Ladewig, that of a woman who died at the age of 60 years of carcinoma of the uterus, the body had gone first to the anatomic institute, where it had been partially dissected before its peculiarities were recognized. His description is therefore limited chiefly to the skull. He concludes that the condition is a congenital and probably hereditary one, characterized by diminished capacity of expansion on the part of the ossification centers, especially those of the membranous bones. Similar but less extremely diminished growth energy is evident in the rest of the skeleton.

O. T. Schultz.

Microbiology and Parasitology

The Postmortem Removal of Liver Tissue from Rapidly Fatal Fever Cases for the Discovery of Silent Yellow Fever Foci. F. L. Soper, E. R. Rickard and P. J. Crawford, Am. J. Hyg. **19**:549, 1934.

The organization of a service for the routine postmortem collection of tissues from the liver in cases of rapidly fatal fever resulted, between May 1930 and June 1933, in the examination of specimens from over twenty-eight thousand livers, and a pathologic diagnosis of yellow fever in fifty-four cases from forty-three places in which yellow fever was not known to be present. A special instrument designed for the rapid removal of hepatic tissue by laymen without autopsy, to which the name "viscerotome" has been given, is described. The routine collection and examination of liver has resulted in: (*a*) the demonstration of typical fatal cases of yellow fever in foci in which otherwise the disease is silently endemic; (*b*) the accumulation of extensive data indicating, so far as negative evidence can indicate, the absence of the yellow fever virus from key centers of population and from hundreds of towns and villages in which antimosquito measures are being applied; (*c*) the confirmation of the occurrence of yellow fever without Aedes aegypti in a small village eleven months after the occurrence of the first suspected case; (*d*) the accumulation of valuable data regarding the distribution of diseases other than yellow fever producing characteristic lesions of the liver.

From the Authors' Summary and Conclusions.

The Microscopical Examination of 29,593 Human Livers from Central and Northern Brazil with Special Reference to the Occurrence of Malaria and Schistosomiasis. N. C. Davis, Am. J. Hyg. **19**:567, 1934.

There have been examined 29,593 specimens of livers from persons dying in central or northern Brazil between May 1, 1930 and June 30, 1933. Most specimens were secured with the viscerotome (described by Soper, Rickard and Crawford: *Am. J. Hyg.* **19**:549, 1934). Malarial pigmentation was recognized in 2,298 specimens. The highest rates of malarial infection were found in Pará, Amazonas and Bahia, in the order given. The lowest rate was in Ceará. The months of greatest incidence were May and June. The age group of highest absolute incidence was that of from 15 to 19 years, although the differences between this group and the two preceding groups (from 5 to 9 and from 10 to 14 years)

were not significant. Lesions caused by Schistosoma mansoni Sambon were recognized in 1,594 livers. The highest rates of schistosome infection were found in Sergipe, Alagôas, Pernambuco and Bahia, in this order. Appreciable rates were found in Parahyba, Espirito Santo and Rio Grande do Norte. In other states the rates were almost negligible. The seasonal fluctuations was less noticeable than those of malaria. The age group of highest incidence was again that of from 15 to 19 years, although the rates did not differ significantly in the groups between the ages of 10 and 29 years. Central necrosis was unduly prevalent in livers with malarial pigmentation and especially so in those with schistosome granulomas. The geographic and seasonal distribution of other cases in which central necrosis was noted suggests that malaria (including blackwater fever) and schistosomiasis may have been responsible for an appreciable proportion of the lesions, even though pigmentation or granulomas were not detected. Lesions of enteric fever and focal necroses of doubtful etiology (many probably typhoid) were especially prevalent among specimens from Ceará. It is explained that this finding was undoubtedly correlated with unsanitary conditions fostered by a severe drought in that state. The rate for miliary tuberculosis was high in the Amazon basin and low in Ceará, Parahyba and Rio Grande do Norte. Various grades of periportal inflammation, with fibrosis shading into marked cirrhosis, were very common.

FROM THE AUTHOR'S SUMMARY.

THE DISTRIBUTION AND EPIDEMIOLOGY OF HUMAN ASCARIASIS IN THE UNITED STATES. G. F. OTTO and W. W. CORT, Am. J. Hyg. **19**:657, 1934.

The evidence presented from our own and other surveys gives a rather clear picture of the distribution of Ascaris in the United States. No endemic centers of importance to public health are recorded for the northern and western parts of the country. In the southeastern states the problem is found among the indigenous population of the Appalachian mountains and the foothills running, south, east and west from the mountains. Certain other centers of infestation are found in south-central Louisiana, in southeastern North Carolina and in the city of Tampa, Fla. For the most part, however, the lowland and costal plain areas of the southern United States have a very low incidence of ascariasis. This rather peculiar distribution of Ascaris in the southern United States can be correlated with the presence or absence of factors favorable to its continued dissemination. These factors have been described at some length and may be summarized under two heads: (1) habits favorable to pollution and (2) climatic conditions.

FROM THE AUTHORS' SUMMARY.

SARCOSPORIDIA IN THE MYOCARDIUM OF A PREMATURE INFANT. A. T. HERTIG, Am. J. Path. **10**:413, 1934.

A case of sarcosporidiosis involving the myocardium of a 26 day old premature infant is reported. This was an incidental observation in the routine microscopic study of postmortem material. The mode of entrance of the parasites into the body cannot be stated with certainty.

FROM THE AUTHOR'S SUMMARY.

EXPERIMENTAL TUBERCULOSIS OF THE BONES AND JOINTS OF RABBITS. PAUL J. TRUDEL, Am. Rev. Tuberc. **28**:331, 1933.

The experimental production of tuberculosis in the bones and joints of rabbits requires delicate technic, but such technic yields good results in 85 per cent of the animals. While only few of the nonsensitized rabbits given injections of human bacilli revealed small tuberculous foci in the lungs and liver, 75 per cent of all the animals first sensitized to and then given infective injections of bovine bacilli showed striking localization in the bones and joints with no detectable focus elsewhere. Only small doses (from 0.05 to 0.15 mg.) should be injected. The bacillary emulsion should be injected into the nutrient artery or the nutrient foramen of

the femur. If the size of the artery does not permit injection, a direct inoculation of the bacilli into the synovial membrane of the knee may be substituted. The bovine type of bacillus gave far better and quicker results than the human type.

H. J. CORPER.

THE VIABILITY AND VIRULENCE OF OLD CULTURES OF TUBERCLE BACILLI. H. J. CORPER and MAURICE L. COHN, Am. Rev. Tuberc. **28**:856, 1933.

In 1919 and 1920 several hundred nursing bottles containing about 3 ounces (90 cc.) of 5 per cent glycerol broth, neutral to litmus, were planted with nineteen different strains of human and bovine tubercle bacilli and were maintained at 37 C. until 1932, when forty-seven bottles containing human bacilli were chosen to determine the viability of the bacilli, and twenty were found to contain bacilli capable of growing on egg yolk medium; of nine bottles planted with bovine bacilli, four contained cultures that were viable in 1932. Twelve of the original seventeen human strains were recovered for study while, of two bovine strains, one was recovered. No growth occurred in transplants from bottles in which the p_H was below 6.1 or above 7.6. About 1 per cent of the bovine bacilli and 0.01 per cent of the human bacilli in the culture masses tested were viable. The virulent strains had not suffered a diminution of virulence during the twelve years' residence in the incubator, and strains of low virulence remained of low virulence during this time. Virulence is a property unchangeable in individual bacilli, but prolonged cultivation on artificial mediums may cause a perceptible, though not striking, change in the progeny of human tubercle bacilli. Persistence of bacilli in the body is dependent on a number of factors, but prominent among these, aside from the pathogenicity of the bacilli, is the factor of the number of tubercle bacilli introduced into the organs and tissues of an animal.

H. J. CORPER.

THE INHIBITORY EFFECT OF NORMAL BLOOD ON THE GROWTH OF TUBERCLE BACILLI. H. J. CORPER and C. B. VIDAL, Am. Rev. Tuberc. **28**:878, 1933.

The growth of human and bovine tubercle bacilli on good mediums is inhibited by normal blood from dogs or rabbits. This inhibition is more evident with small numbers than with large numbers of bacilli and is more evident on inspissated egg yolk than on potato. The effect is due to the development of toxic autolytic products from normal blood, and is absent when the blood has been treated with one or two volumes of 6 per cent sulphuric acid for from one-half to one hour at 37 C., which destroys the autolytic enzymes, followed by neutralization with isotonic sodium bicarbonate solution (or other nontoxic alkalies). Regardless of the treatment, however, accurate determination of the number of tubercle bacilli placed in blood is not possible by counting the colonies which this blood will yield on good mediums suited to growing small numbers of human and bovine tubercle bacilli from the suspensions.

H. J. CORPER.

THE EFFECT OF ANIMAL PASSAGE ON THE VIRULENCE OF TUBERCLE BACILLI. HENRY STUART WILLIS, Am. Rev. Tuberc. **28**:884, 1933.

An account is given of the passage of a strain of tubercle bacilli (RI) of low virulence through guinea-pigs for a period of ten years. This required fifty-seven passages. During this prolonged period progressive diseases appeared three times, in three of about nine hundred animals used. Whether the disease in these instances was an extraneous, contaminating tuberculosis could not be determined. That it was is possible if not probable. But for these three exceptions passage appeared to have no effect on the virulence of the strain used. A strain of virulent tubercle bacilli was carried in animals for more than eight years through fifty passages with evidence of a slight increase of virulence. This strain carried on artificial mediums during the same eight-year period lost considerably in virulence

but is still fully capable, in small doses, of leading to the death of guinea-pigs. It appears that a prolonged stay of weakly virulent tubercle bacilli in animal tissues does not as a rule affect the virulence.

H. J. CORPER.

PATHOLOGICAL FINDINGS AND PATHOGENESIS OF CONGENITAL TUBERCULOSIS. MORRIS SIEGAL, Am. Rev. Tuberc. **29**:297, 1934.

Siegal reports on the findings recorded in thirty-eight cases of undoubted or probable congenital tuberculosis. The tuberculous organs were usually the lungs, liver and spleen and, after a certain age, the intestines. Macroscopically the lesions almost always resembled tubercles. Microscopically they were reported as tubercles, except those in the lungs, where tuberculous pneumonic areas were not uncommon. Caseation was common; cavitation, ulceration and calcification were also mentioned. In the few cases in which primary lesions were specifically reported, they were described as localized caseous areas in the lungs or the liver and in one instance as a diffuse bilateral tuberculous bronchiolitis and alveolitis with beginning caseation. The lungs were most frequently involved. The degree of pulmonary involvement was usually equal to and occasionally greater than that of the liver. In cases in which death occurred in the latter half of the first month of life, the lungs and regional lymph nodes were usually alone involved. Involvement of the liver and spleen went side by side, these organs usually being involved in the same cases and to the same degree. The liver was most frequently involved and to the greatest degree in cases in which death occurred in the first two weeks of life, least involved in those in which death took place in the second half-month of life, and usually involved in cases in which death occurred subsequently to this. Tuberculous lesions in the gastro-intestinal tract were seen in 70 per cent of infants of 39 days or older, all of whom had advanced pulmonary tuberculosis. No undoubted cases were reported in infants less than 39 days of age. The lymphatic nodes usually involved were the pulmonary, mesenteric and portal in diminishing frequency. Acute tuberculous leptomeningitis was reported in only one case.

H. J. CORPER.

TUBERCLE BACILLI IN THE GASTRIC CONTENTS OF TUBERCULOUS CHILDREN. INA GOURLEY, Am. Rev. Tuberc. **29**:461, 1934.

Fifty-nine cases of tuberculosis in childhood were studied by gastric lavage and the inoculation of guinea-pigs. All the children reacted positively to the intracutaneous injection of tuberculin. In fifty cases lesions of the lungs were demonstrable in roentgenograms. In nine there were no demonstrable lesions. In twenty-eight cases (47.7 per cent) tubercle bacilli were found in the gastric contents. Of the fifty children with demonstrable lesions, twenty-eight (56 per cent) had the bacilli in the gastric contents. Fourteen, or 50 per cent, of the children with the bacilli in the gastric contents were of school age. The study apparently indicates that in tuberculosis of childhood all types of parenchymal lesions, including those of the "C" group of McPhedran's classification (McPhedran, F. M.: Classification of Tuberculous Pulmonary Lesions in Childhood and Adolescence, Am. Rev. Tuberc. **20**:532, 1929), are "open."

H. J. CORPER.

EFFECTS OF TUBERCULO-PROTEIN (MA-100) ON THE COURSE OF TUBERCULOSIS IN RABBITS AND GUINEA PIGS. J. C. SMITHBURN, F. R. SABIN and J. T. GEIGER, Am. Rev. Tuberc. **29**:562, 1934.

Both rabbits and guinea-pigs, when subjected to a long series of daily injections of tuberculoprotein, became hypersensitive to this substance, as indicated by their intracutaneous reactions. Accompanying this induced hypersensitiveness there was an abolition of the response in temperature induced by the protein. Little or no effect on resistance to tuberculosis in either rabbits or guinea-pigs was produced by the tuberculoprotein.

H. J. CORPER.

UNDULANT FEVER DUE TO BRUCELLA SUIS. C. P. BEATTIE and R. M. RICE, J. A. M. A. **102**:1670, 1934.

In a milk-borne outbreak of undulant fever thirty cases occurred. Twenty-seven of the patients obtained their milk from the same dairy. The dairy, from a herd of twenty cows, supplied approximately eighty households; in eighteen of these, cases of undulant fever developed. Brucella suis was obtained in blood culture from six of fourteen patients and from the milk of one of the cows in the herd. The outbreak ceased thirteen days after the stoppage of the sale of milk from the dairy. There is a greater virulence of Brucella suis than of Brucella abortus. The possibility of milk containing Brucella suis must be considered.

FROM THE AUTHORS' SUMMARY.

RAT-BITE FEVER ACQUIRED FROM A DOG. H. S. RIPLEY and H. M. VAN SANT, J. A. M. A. **102**:1917, 1934.

Spirillum morsus-muris has been isolated from two cases of rat-bite fever. The animal vector was apparently a dog. The disease has been produced in dogs. The Kahn reaction was strongly positive in both patients and in the dog that survived, while the Kolmer-Wassermann reaction was usually negative or weakly positive. A patient with dementia paralytica was inoculated with the spirillum, and a typical lesion and symptoms of rat-bite fever developed. Flagella were demonstrated only with Burri's india ink method. The mouse proved to be a better diagnostic animal than the guinea-pig. In one case, infection was contracted when no abrasion of the skin was noted, suggesting ease of penetration by the organism. The clinical course of the disease showed marked variation. A course of from three to six treatments with arsphenamine seems advisable.

FROM THE AUTHORS' CONCLUSIONS.

THE VARIANT AND FILTERABLE FORMS OF CERTAIN GREEN-PRODUCING STREPTOCOCCI. R. A. MCKINNEY, J. Bact. **27**:373, 1934.

Rapid serial transfers of rough or smooth green-producing streptococci on a single medium induce a change in colony type but no change in morphology. Streptococci aged in unfavorable or in stimulating mediums and then subjected to repeated transfers on mediums of differing physical and chemical states produce variant colonies containing morphologically variant cells. Pleomorphic green-producing streptococci give rise by described technics to three variants—(1) a blood-bleaching, nitrite-forming diplococcus in rounded, moderately rough colonies, (2) a diphtheroid in gray or yellow mucoid colonies, and (3) a proteolytic spindle-shaped rod in definitely rough colonies. The diplococcus and the diphtheroid possess antigenic structures and biochemical functions differing from each other and from those possessed by the original streptococcus. Diplococci and diphtheroids so formed give rise again to streptococci by a process which is preceded by and probably depends on a changed mode of cell division. The streptococcus thus recovered resembles, but is not identical with, the original streptococcus in serologic properties and biochemical action. A precipitate containing viable forms occasionally develops in the filtrates of streptococcic cultures. This occurs when atypical cell division, chain reduction and granule formation are clearly evident in the culture before filtration. The viable forms eventually by a suitable technic assume a visible form, in most cases that of a diplococcus similar to the one isolated from the same culture before filtration. In two cases diplococci from the filtrates were converted to streptococci with attributes similar to but not identical with those of the original strains of streptococci.

FROM THE AUTHOR'S CONCLUSIONS.

LEISHMANIA DONOVANI IN NASAL AND ORAL SECRETIONS OF KALA-AZAR. C. E. FORKNER and L. S. ZIA, J. Exper. Med. **59**:491, 1934.

Smears from the nasal cavities of fifteen patients suffering from kala-azar have been examined, and in those from nine of the patients typical Leishman-Donovan

bodies have been found. Smears from the surface of the tonsil and from the saliva of one of these nine patients showed Leishmania. The tonsils of this patient, who died as the result of kala-azar and secondary infection, were shown at autopsy to be massively infected with Leishman-Donovan bodies. Leishmania in the nasal discharges of two patients was shown, by inoculation into susceptible animals, to be viable and capable of producing infection. Sufficient time has not elapsed to determine the viability of the organisms in the remaining cases. These experiments show for the first time that in a large proportion of patients with kala-azar there is available a rich source of infective material for direct transmission of the disease. Strong evidence is presented that one of the natural routes, perhaps the most important natural route, of transmission of kala-azar is that from person to person by way of the upper respiratory and alimentary tracts. In two normal human volunteers and numerous normal experimental animals Leishmania has been inoculated into the nasal and oral cavities with the nasal discharge, known to contain Leishmania, from patients with kala-azar. The results of these experiments will be reported at a subsequent date.

FROM THE AUTHORS' SUMMARY AND CONCLUSIONS.

Immunology

SKIN REACTION TO TUBERCULIN PROTEINS IN HODGKIN'S DISEASE. P. E. STEINER, Arch. Int. Med. **54**:11, 1934.

Tuberculin protein (Seibert) was used in intracutaneous tests on thirty-five patients with Hodgkin's disease and on thirty-eight controls with a variety of lymphoma. Tuberculin proteins prepared from both avian and human strains were used. No evidence of specific sensitization to the avian tuberculin protein was obtained. A marked desensitization (or absence of sensitization) was found to both proteins in the patients with Hodgkin's disease. This relative absence of "normal adult sensitization" was of diagnostic value, especially in the differential diagnosis of tuberculous adenitis. The interpretation is made that either (1) the process of Hodgkin's disease desensitizes its victims to these tuberculin proteins or (2) Hodgkin's disease usually occurs in persons in whom development of the normal sensitization to the tuberculin protein is impossible. It is difficult to conceive of either of these phenomena as occurring in a disease unrelated to tuberculosis.

FROM THE AUTHOR'S SUMMARY.

PATHOLOGIC HISTOLOGY OF THE SHWARTZMAN PHENOMENON. H. T. KARSNER AND A. R. MORITZ, J. Exper. Med. **60**:37, 1934.

Histologic study of the reaction to an injection of the preparatory factor of the Shwartzman phenomenon shows this reaction to be an exudative inflammation, but furnishes no conclusive evidence as to whether or not it is conditioned by previous sensitization to substances contained in the bacterial filtrate. Histologic study of the local reaction which follows an intravenous injection of the reacting or provocative factor shows an exudative inflammation which differs from that due to the preparatory factor principally in the increased general severity and the marked damage to blood vessels. The increased severity is probably due to a concentration of the injurious agent at the site of inflammation determined by the preparatory local injection. The exudative phenomena caused by the preparatory local injection are edema and infiltration by polymorphonuclear leukocytes and large mononuclear cells. Vascular injury is morphologically demonstrable in only a few of the sections, notably those from periarticular structures. The intravenous injection determines an increase in cellular infiltration, necrosis of exudate, phagocytosis of cell débris, destruction of vascular walls and hemorrhage. Healing is due to granulation, organization and cicatrization.

FROM THE AUTHORS' CONCLUSIONS.

CHEMO-IMMUNOLOGICAL STUDIES ON CONJUGATED CARBOHYDRATE-PROTEINS. W. F. GOEBEL, F. H. BABERS and O. T. AVERY, J. Exper. Med. **60**:85, 1934.

The results of the present study not only confirm the view previously held that the immunologic specificity of carbohydrates is determined by their stereochemical configuration, but lend support to the further assumption that the introduction of a simple chemical group, such as the acetyl radical, endows a carbohydrate with a new and distinct specificity which is determined by the chemical nature of the group thus introduced. It has been previously pointed out that the differences in the specific behavior of the alpha- and beta-glucosides of glucose may be accounted for by differences in the stereochemical configuration of the carbon atom bearing the aglucon, and that the basis for the immunologic crossing may lie in the fact that the spatial configuration of the polar groups on the remaining five carbon atoms is identical. This explanation appears to be further supported by the results of the present study. For it can be seen from table 2 that when beta-gluco-test antigen, which normally reacts in alpha-gluco-globulin antiserum, is so altered that one of the polar groups (OH) of the five terminal carbon atoms of the carbohydrate radical is replaced by acetyl (CH_3CO), the resulting antigen fails to react in alpha-gluco-globulin antiserum. Furthermore, alpha-gluco-test antigen, which normally reacts with beta-gluco-globulin antiserum, fails to react in the immune serum produced by immunization with acetyl beta-gluco-globulin. Similarly, the acetylated beta-glucoside, owing to the alteration in chemical constitution, fails to bind the antibody in alpha-gluco-globulin antiserum, and as a result permits both alpha- and beta-gluco-test antigens to react in their normal course. The beta-glucoside likewise fails to inhibit the reaction between the acetyl beta-gluco-test antigen and homologous immune serum. This difference in the serologic specificity of the antibodies induced by beta-gluco-antigens in the acetylated and unacetylated form can be attributed only to the known differences in the chemical structure of these two glucosides. The latter differ from one another in that the acetyl beta-glucoside is a derivative in which one of the polar groups (OH) of the carbohydrate has been altered by the introduction of an acetyl radical (CH_3CO). A critical analysis of the results of these serologic tests again emphasized the fact that the presence of an acetyl group in a carbohydrate exerts a determining influence on the specificity of an antigen of which it forms a part. In conclusion it may be pointed out that the differences in serologic specificity exhibited by the acetylated and deacetylated polysaccharides of Pneumococcus type I are accurately paralleled by the purely synthetic system described.

FROM THE AUTHORS' DISCUSSION.

THE ANTIGENIC RELATIONSHIP BETWEEN PROTEUS X-19 AND TYPHUS RICKETTSIA. M. R. CASTANEDA, J. Exper. Med. **60**:119, 1934.

A soluble specific substance was isolated from the rickettsiae of Mexican typhus which gave, with Proteus X 19 antiserum and human typhus serum, the same precipitation reactions as the polysaccharides extracted from Proteus OX 19. The soluble specific substance extracted from the rickettsiae and Proteus OX 19 is likely to be of a polysaccharide nature, as judged by the strong Molisch reactions obtained with such extracts, the heat stability and the negative protein reactions (biuret). Since, however, it still contains 7 per cent nitrogen, this is not certain. In the antigenic composition of Proteus X 19 and typhus rickettsiae there is a common soluble specific factor which is responsible for the Weil-Felix reaction.

FROM THE AUTHOR'S SUMMARY AND CONCLUSIONS.

THE A SUBSTANCE OR ACETYL POLYSACCHARIDE OF PNEUMOCOCCUS TYPE I. J. F. ENDERS AND C-J. WU, J. Exper. Med. **60**:127, 1934.

Since the evidence obtained in the course of this study indicates that the A carbohydrate of Pneumococcus type I (Enders, J.: *J. Exper. Med.* **52**:235, 1930) and the acetyl polysaccharide of Avery and Goebel (*J. Exper. Med.* **58**:731, 1925)

represent the same chemical substance, it is suggested that the designation "A carbohydrate" or "A substance" be relinquished in favor of the more exactly descriptive term "acetyl polysaccharide."

VACCINATION OF MONKEYS AND LABORATORY WORKERS AGAINST PSITTACOSIS. T. M. RIVERS AND F. F. SCHWENTKER, J. Exper. Med. **60**:211, 1934.

Monkeys that have recovered from psittacosis pneumonia have an increased resistance to infection with the virus and possess neutralizing antibodies in their serum. Large amounts of the active virus can be introduced intravenously and intramuscularly into monkeys without the production of a serious infection such as pneumonia. Relatively small amounts of the virus introduced intratracheally into monkeys usually lead to psittacosis pneumonia. Monkeys vaccinated intramuscularly with the unattenuated virus have an increased resistance to the active agent and possess neutralizing antibodies in their serum. The intramuscular introduction of the active virus in moderate amounts into human beings is relatively harmless, and repeated inoculations lead to the appearance of neutralizing antibodies in the serum of the vaccinated persons.

FROM THE AUTHORS' SUMMARY.

THE IMMUNOLOGICAL CHARACTERISTICS OF THE POLIOCIDAL SUBSTANCE IN HUMAN SERUM. C. W. JUNGEBLUT, J. Immunol. **27**:17, 1934.

Quantitative titrations of pooled serums of normal human adults and of adults convalescent from poliomyelitis revealed no fundamental differences in virucidal titer in the case of blood groups A and B. Normal serums of blood group O, on the other hand, slightly exceeded in potency the corresponding convalescent serums. The temperatures which destroyed the virucidal principle in normal and convalescent serums of the same blood groups were practically identical. The thermostability of a given serum varied in direct proportion to its virucidal titer. The virucidal substance could not be removed from either normal or convalescent serum by contact with virus in vitro. In several instances, however, absorption was observed after contact with various red cells. Neutralization of the virus in vitro was obtained with certain samples of antidiphtheritic, antistreptococcic and antisnake serum from the horse. In contrast to this, a large number of other immune horse and rabbit serums—antibacterial, antitoxic and antiviral—failed to inactivate the virus. Immunization of monkeys with diphtheritic toxoid or a toxin-antitoxin mixture increased the resistance of nearly one half of the animals in various degrees to subsequent poliomyelitic infection. Virucidal substances were demonstrable in some of the serums of completely or partially protected monkeys.

FROM THE AUTHOR'S CONCLUSIONS.

INACTIVATION OF POLIOMYELITIS VIRUS AND OF DIPHTHERIA TOXIN BY ENDOCRINE PRINCIPLES. C. W. JUNGEBLUT, K. MEYER AND E. T. ENGLE, J. Immunol. **27**:43, 1934.

The virus of poliomyelitis was inactivated in vitro by certain biologic products of human and animal origin containing anterior pituitary-like principles and by the suprarenal cortical and medullary hormones. Diphtheritic toxin was inactivated in vitro by preparations of the urine of pregnancy and by suprarenal cortical hormone.

FROM THE AUTHORS' SUMMARY.

THE AUTONOMIC NERVOUS SYSTEM IN THE ANAPHYLACTIC SMOOTH MUSCLE CONTRACTION. C. V. SEASTONE JR. and A. ROSENBLUETH, J. Immunol. **27**:57, 1934.

From the results reported it is evident that the contraction of the nictitating membrane of the cat furnishes a convenient criterion of anaphylactic shock in that animal. Since the smooth muscle concerned in these experiments was totally denervated, it is evident that the contraction during shock may occur without the

mediation of autonomic nerve impulses. The effectors are then directly excited during shock as they are by suprarenin, histamine and other substances.

From the Authors' Discussion and Conclusions.

The Effect of Reticulo-Endothelial Cell Blockade upon Antibody Formation in Rabbits. L. Tuft, J. Immunol. **27**:63, 1934.

In rabbits efficient and continued blockade of the cells of the reticulo-endothelial system by such inert particulate material as india ink or trypan blue prevents the formation of agglutinins against Bacillus typhosus and Bacillus paratyphosus A and B and of complement-fixing antibodies against B. typhosus, and thus supplies further evidence of the importance of this system in the formation of these antibodies. The effect is independent of the route of administration of the antigen, as long as the dose of the antigen is not too large to cause excess stimulation. While the amount of particulate matter necessary for efficient blockade may vary with the type of antigen used and its affinity for the reticulo-endothelial cells, nevertheless the principle of continued saturation of these cells throughout the course of the experiment to prevent regeneration of new cells is essential for satisfactory results.

From the Author's Conclusions.

Electric Charge of Bacteria Sensitized with Purified Agglutinins. L. Olitzki, J. Immunol. **27**:105, 1934.

The H-forms of Bacillus proteus show a higher velocity of migration to the anode than do the corresponding O-forms. Agglutination with pure H-agglutinin reduces the charge of the agglutinable H-forms, while the inagglutinable O-forms in the same culture are not affected. Agglutination with pure O-agglutinin reduces the charge of the O-forms, the H-forms of the bacteria remaining unaffected. Agglutination with serum containing both types of agglutinins reduces the charge of all the cells present in the suspension. Below p_H 4 the H-antigen was destroyed and H-agglutination did not occur. The bacteria treated with purified H-agglutinin were not agglutinated and showed the same anodic migration as unsensitized bacteria. Amphoteric protein-like behavior of bacteria, that is, a positive charge below the iso-electric point, was observed only after treatment with large amounts of nonpurified antiserum. After treatment with purified O-agglutinin or after washing the sensitized bacteria free from serum, cathodic migration below p_H 4 was not observed.

From the Author's Conclusions.

The Sensitization of Guinea Pigs to Poison Ivy. F. A. Simon and others, J. Immunol. **27**:113, 1934.

Guinea-pigs can be made sensitive to poison ivy by rubbing a 10 per cent extract in petrolatum into their skin or by painting the normal skin with a strong extract. When, however, the extract is painted on the active lesions produced by the virus of cowpox the resulting sensitiveness is less marked. The response of the skin has been injured. When the extract is injected intravenously or intraperitoneally no cutaneous sensitiveness results. When one area of skin is sensitized, all the skin is sensitized. The production of a cutaneous sensitiveness to poison ivy has been accomplished so far only by treatment of the skin itself. These experiments give further support to the theory that the sensitiveness of man to poison ivy is acquired by virtue of previous contact with the plant.

The Antigenic Value of the "Fixed" Virus of Rabies Inactivated by Photodynamic Action. I. A. Galloway, Brit. J. Exper. Path. **15**:97, 1934.

The fixed virus of rabies is sensitive to the photodynamic action of methylthionine chloride (methylene blue). Under the conditions of the experiments it was inactivated in collodion-membrane or sand and paper-pulp filtrates but not in unfiltered suspensions. The virus appears to be relatively more sensitive to the

photodynamic action of proflavine than to that of methylthionine chloride, at least in the presence of physiologically active cells or portions of cells from an infected animal. It was inactivated by irradiation when the former dye was employed even in unfiltered suspensions of fresh infected brain. The fixed virus inactivated by the photodynamic action of methylthionine chloride or proflavine conserves its antigenic potency, since about twenty-six of thirty-one rabbits—84 per cent—which had received more than one dose of such a vaccine survived an intramuscular test dose of fresh virus, while of sixteen unvaccinated control animals only one survived (percentage of survival, 6). FROM THE AUTHOR'S SUMMARY.

IMMUNIZING FRACTIONS FROM BACT. AERTRYCKE. H. RAISTRICK AND W. W. C. TOPLEY, Brit. J. Exper. Path. **15**:113, 1934.

In summary, we think it has been demonstrated that fractions can be isolated from Bacterium aertrycke, and inferentially from other organisms, that contain the specific somatic polysaccharides in an antigenically active form in the absence of any intact protein. Such fractions are toxic, and are efficient immunizing agents, inducing an active antibacterial and antitoxic immunity associated with the production of specific precipitating and agglutinating antibodies. The distribution of toxicity among the various fractions runs closely parallel to the distribution of immunizing potency. Whether this indicates that the toxic and immunizing substances are identical, or whether we are dealing with two or more different substances that behave in the same way to the reagents we have employed, or with an association resulting from adsorption, are problems that await further solution. It need hardly be added that there would be no justification for the assumption that the toxic and immunizing substances present in our fractions represent the total toxic and immunizing potentialities of the bacterial cells. The fractions with which we have been concerned are certainly not chemically pure substances, and we do not think that the evidence at present available, although indicative of the presence of a phosphatide as well as a polysaccharide, allows any final conclusion to be reached as to the exact structure of the complete antigenic molecule of which the polysaccharide forms a part. FROM THE AUTHORS' SUMMARY.

BLOOD-SUGAR CHANGES AND TOXIC EFFECTS PRODUCED IN RABBITS BY FRACTIONS FROM BACT. AERTRYCKE. M. E. DELAFIELD, Brit. J. Exper. Path. **15**:130, 1934.

Fractions containing polysaccharide components but no unaltered protein, derived from the bodies of Bacterium aertrycke by tryptic digestion followed by alcohol precipitation, are active in producing hyperglycemia and toxic effects in rabbits. The toxicity of the various fractions tested runs closely parallel to their ability to induce antibacterial and antitoxic immunity in mice. These active fractions are all precipitable within the range of from 50 to 68 per cent by weight of alcohol concentration. The fraction obtained by excess alcohol after removal of the 68 per cent fraction is inactive, as is also the alcohol-soluble material. Acid or alkali hydrolysis of the alcohol precipitate designated F68/68 destroys the power to produce hyperglycemia. Immunity to the chemical response can be developed by a series of injections of the alcohol fraction F68/68.

FROM THE AUTHOR'S SUMMARY.

THE IMMUNIZING ACTION OF EXTRACTS OF PNEUMOCOCCI (TYPES 1 AND 2). D. HARLEY, Brit. J. Exper. Path. **15**:161, 1934.

Extracts of pneumococci (types 1 and 2) made by the action of twentieth-normal hydrochloric acid at 60 C. for fifty minutes produce active type-specific immunity in mice and type-specific agglutinins and protective antibodies in rabbits. Heating the extracts to 100 C. at p_H 4-5 does not impair their immunizing action for mice, but similar treatment at p_H 9-10 inactivates them. The relationship of the active principles of these extracts to the immunizing antigen of the intact

pneumococcus and to the acetyl polysaccharide of type I pneumococci (Avery and Goebel: *J. Exper. Med.* **58**:731, 1925) is discussed.

FROM THE AUTHOR'S SUMMARY.

EXPERIMENTS WITH THE "O" ANTIGEN OF CLOSTRIDIUM OEDEMATIS MALIGNI (VIBRION SEPTIQUE). D. W. HENDERSON, Brit. J. Exper. Path. **15**:166, 1934.

Active immunity can be obtained against Clostridium oedematis-maligni by the use of pure "O" antigen. The immunity is type-specific. A common "O" antigen, however, is shared by strains in varying degree and is effective in producing minimal degrees of cross-infection. In immunized animals the reaction to infection is generally associated with a severe local perforating gangrene. The "O" antigen functioning in agglutination and complement fixation is directly responsible for the production of the protecting immune body. A classification of strains of Cl. oedematis-maligni is suggested. The basis of the primary differentiation should be the "O" antigen relationship, and the "H" antigen content should form the basis of a secondary grouping.

FROM THE AUTHOR'S SUMMARY.

THE PROBLEM OF NATURAL RESISTANCE IN THE WHITE RAT. E. DE BALOGH, Ann. d'anat. path. **10**:65, 1933.

Having previously shown that human tubercle bacilli injected into normal tissues of the white rat produced no damage, whereas when injected into transplantable tumors of this animal they produced necrosis and ulceration, the author made similar experiments with B C G. The same necrosis and ulceration resulted. Tumor tissue thus appears to be a susceptible portal of entry for an infection against which the animal is normally resistant. The experiment was repeated with Bacillus proteus, Bacillus pyocyaneus, Bacillus diphtheriae, Bacillus typhosus and Bacillus coli, and the same results were obtained. The necrosis following these injections occurred much more rapidly and was more intense than spontaneous necrosis in such tumors. Occasionally following such an injection the tumor would undergo complete necrosis, slough out and heal completely. The poor resistance of tumor tissue is not due to absence of inflammatory reaction, because such substances as turpentine, glycerin, iodoform, etc., when injected produce marked inflammatory changes in the stroma. It is more logical to believe that tumor tissue approaches the anergic state of embryonic tissue. Thus tumor tissue resembles embryonic tissue not only in its histologic and biochemical characters, but also in immunologic characters.

PERRY J. MELNICK.

Tumors

MYXOMA OF THE HEART VALVES. T. C. JALESKI, Am. J. Path. **10**:399, 1934.

Whether the myxomas are neoplasms or whether they represent a degenerative process in connective tissue growths is still open to question.

MICROSCOPIC METASTASES IN THE THYROID GLAND. C. O. RICE, Am. J. Path. **10**:407, 1934.

In eighty-nine necropsies in cases of malignant growth tumor cells were found in the thyroid gland in nine. In five of these nine cases there were macroscopic secondary nodules; in the remaining four cases the metastases were microscopic only.

PARASELLAR MENINGEAL FIBROBLASTOMA ARISING FROM THE SPHENOID RIDGE. B. J. ALPERS and R. A. GROFF, Arch. Neurol. & Psychiat. **31**: 713, 1934.

Aside from intrasellar and suprasellar tumors, Alpers and Groff recognize parasellar tumors. These tumors are situated near the sella turcica and arise from

the sphenoid ridge, bearing a relationship to the lesser or greater wings of the sphenoid bone. They are encapsulated, lobulated in appearance and adherent to the dura, which they may invade. They may become calcified, extend to the middle and the anterior cranial fossa and compress the neighboring structures (second or third nerve, the internal carotid artery, the middle and anterior cerebral vessels). The tumors of the lesser wing are easy to diagnose; those of the greater wing give an indefinite clinical picture. Six of the tumors described resembled more or less typical meningeal fibroblastoma. Three were less typical.

G. B. HASSIN.

LYMPHOSARCOMA IN BONE. L. F. CRAVER and M. M. COPELAND, Arch. Surg. **28**:809, 1934.

One hundred and sixty-four patients with lymphosarcoma have been studied. Seventeen patients (10.4 per cent) were found to have involvement of the bones. The bones most frequently involved were those of the spine and pelvis. Pathologic fracture was observed five times. Collapse of the vertebrae was relatively rare. Signs of compression of the cord were noted in three patients. Two types of osseous changes were noted: osteolytic and osteoplastic. Osteolytic changes predominated. A combination of both was seen occasionally. Two routes of involvement of the bone were observed: (1) the hematogenous and (2) direct infiltration from contiguous diseased lymph nodes. The histologic studies showed all the specimens to be reticulum cell lymphosarcomas. The stomach was involved by lymphosarcoma in two cases; the ileum, in one case. All the patients except one had evidence of involvement of the lymph nodes prior to demonstrable osseous changes. In two patients a low grade lymphatic leukemia developed prior to death. Histologically the lymph nodes showed typical lymphosarcoma.

FROM THE AUTHORS' SUMMARY.

PRIMARY OSTEOGENIC SARCOMA OF THE THYROID GLAND. A. C. BRODERS and J. DEJ. PEMBERTON, Surg., Gynec. & Obst. **58**:100, 1934.

This rare tumor occurred in a man 71 years of age. It was firmly adherent to the trachea, larynx and blood vessels, and consisted of polymorphic sarcoma cells, osteoid tissue and fully differentiated bone.

W. C. HUNTER.

PRIMARY CARCINOMA OF THE URETER. W. W. SCOTT, Surg., Gynec. & Obst. **58**:215, 1934.

Primary carcinoma of the ureter is a relatively rare disease, there being only sixty-one acceptable cases recorded in the literature. The most common type of tumor is the papillary carcinoma. The disease occurs with equal frequency in the fifth, sixth and seventh decades of life. The average age of the patients in this series was 55.7 years. The right ureter seemed to be involved slightly more frequently than the left, and the lower third of the ureter was involved in 57 per cent of the cases. Increased knowledge concerning the behavior of this disease, as well as the marked advances in the technic of urologic diagnosis, should result in earlier diagnosis.

FROM THE AUTHOR'S SUMMARY (W. C. HUNTER).

THE PRODUCTION OF DIBENZANTHRACENE TUMORS IN PURE STRAIN MICE. H. B. ANDERVONT, Pub. Health Rep. **49**:620, 1934.

The results of the experiment confirm the findings of Burrows, Hieger and Kennaway in showing that the subcutaneous injection of a dibenzanthracene-lard solution induces sarcomas in mice. In addition, it has been shown that this solution induces tumors in pure strain mice in which, under normal conditions, spontaneous tumors do not develop. Thus it is shown that the genetic constitution of a pure strain of mice does not prevent the cells from becoming malignant when exposed to

this carcinogenic agent. Transmission experiments demonstrate that the induced tumors grow only in mice of the same strain in which they originated. In this respect they are similar to spontaneous tumors arising in pure strain mice.

FROM THE AUTHOR'S SUMMARY.

THE INFLUENCE OF ISCHAEMIA ON THE DEVELOPMENT OF TUMOURS. JOHN W. ORR, Brit. J. Exper. Path. **15**:73, 1934.

Fibrous scar tissue was produced in the subcutaneous tissues of mice by the insertion of linen thread sutures, which were subsequently removed, and healing was allowed to take place. Care was taken to avoid direct injury to the epithelium. Tar applications induced tumors more rapidly in these mice than in controls, and histologic examination showed that the percentage of carcinoma at the twenty-first week was twice that in the controls. Local injection of vasoconstrictor drugs produced an acceleration in the induction of tumors, more marked with epinephrine hydrochloride than with ephedrine sulphate. Carcinoma was increased in mice treated with epinephrine, but not significantly in those treated with ephedrine, as compared with controls receiving injections of salt solution and nontreated controls, at the twenty-first week of tarring. Tumors appeared more rapidly than usual where tar was applied after discontinuance of a series of injections of ephedrine sulphate. The results are discussed in relation to other work and certain concomitant conditions in cases of human cancer, and the opinion is expressed that carcinogenic agents act on cells which have been deprived of a fully adequate vascular supply.

FROM THE AUTHORS' SUMMARY.

AN ATTEMPT TO PRODUCE IMMUNITY TO INDUCED TUMOURS IN MICE. F. C. PYBUS, Brit. J. Exper. Path. **15**:89, 1934.

The development of tar tumors was neither prevented nor delayed in mice which had received various numbers of inoculations of mouse embryo skin. Accordingly, the injection of skin has no protective action against the genesis of an induced tumor. Inoculations of mouse embryo skin continued after the appearance of tar tumors had no curative effect, and the tumors did not regress. The numbers of metastases found in the control mice were so much greater than those found in the inoculated mice that it is suggested that the inoculations of skin, although useless for producing an immunity to induced tumors, do develop a resistance in the animal against the metastatic spread of malignant cells.

FROM THE AUTHORS' SUMMARY.

IMMUNITY IN ROUS FOWL SARCOMA AND ITS BEARING ON THE PROBLEM OF THE NATURE OF NORMAL AND CANCEROUS GROWTH. M. J. A. DES LIGNERIS, Publ. South African Inst. M. Research **6**:1, 1934.

"Finally, coming back to the tumour which has been investigated in our experiments, the Rous sarcoma, we have adopted the view that the agent, being in an intermediate position between the 'living and the dead,' unites with some part of the protoplasm of a congenial normal cell, and that this combine constitutes a somewhat new, alienated, living protoplasm, capable of metabolizing, of increasing at the expense of the protoplasm. Finally, the whole cell is taken up by 'tumour protoplasm' and we have a tumour cell of the malignant type, the assumed behavior of which (antigenic character, leading to antibody production by the organism and to retaliatory measures of self-defence and aggression by the tumour cell) we have just outlined.

"It may be said that this conception of tumours, leading from the normal cell, by intermediate stages up to the highly malignant Rous sarcoma cell, is not proved, that is only a hypothesis. We do not deny that we cannot by means of chemical formulae or mathematical deductions prove our case. In fact, such possi-

bilities are very rare in biology; but it is thought that, as no known facts are in conflict with this hypothesis, and as we know of no other hypothesis which would allow of such an easy explanation of all growth processes, without exception, we are fully permitted to use it as a working hypothesis, not only for theoretical discussions, but for the building up of practical deductions which should form a reasonable approach to research work on the prophylaxis of cancer."

ANILINE TUMORS IN THE INDUSTRIAL REGION OF BASEL. A. MÜLLER, Schweiz. med. Wchnschr. **14**:951, 1933.

Thirty-six cases of carcinoma of the bladder have been observed by Müller in chemical workers since 1912. The ages of the patients were from 22 to 77 years. The chemicals to which the workers were exposed by inhalation were amines of the aniline series. The average time from the beginning of exposure to the recognizable development of the tumor was sixteen years; the minimum time was six years. In these cases the carcinoma arose in the floor or walls of the bladder.

JACOB KLEIN.

"MYOBLASTOMA" OF THE DIAPHRAGM. W. MÜLLER, Centralbl. f. allg. Path. u. path. Anat. **58**:353, 1933.

The growth reported occurred on the right leaf of the diaphragm, was 10 by 7 by 4 cm., attached by a stalk 4 cm. in diameter, so that it was freely movable in the pleural cavity, and entirely covered with pleura. Microscopically the mass was heterogeneous, but most portions contained several well defined cell types. Strained muscle in bundles surrounded by thin connective tissue was evident, as were also regions rich in round or spindle-shaped cells with large nuclei, some of which contained mitotic figures. Typical myoblasts were not seen, but the author believes that the tumor should be classified as a malignant myoblastoma or myoblastic sarcoma.

GEORGE RUKSTINAT.

Medicolegal Pathology

HUMAN THALLOTOXICOSIS. J. C. MUNCH, J. A. M. A. **102**:1929, 1934.

An extensive search of the literature prior to January 1934 has been made to learn the extent of human poisoning from thallium compounds and the number of deaths resulting therefrom. In the course of industrial exposure, 12 persons have been poisoned, but none has died. During clinical use, 692 persons have been affected and 31 have died. Toxicologic literature records 53 human beings poisoned by thallium compounds, with 10 deaths. Following rodenticidal and entomologic use, 21 human beings have been poisoned and 5 have died. Reports have been found of 778 human beings poisoned with thallium compounds; 46 (6 per cent) died with thallotoxicosis.

FROM THE AUTHOR'S SUMMARY.

SPONTANEOUS DISLOCATION OF THE ATLAS. F. A. R. STAMMERS and PHILIP FRAZER, Lancet **2**:1203, 1933.

Forward dislocation of the atlas on the axis is not exceptionally rare. It does not necessarily prove fatal, though it is more likely to do so if the odontoid process remains intact. Though usually associated with trauma (and this sometimes quite trivial) it may be essentially spontaneous, occurring during the course of: (*a*) acute rheumatic fever in any of its clinical forms; (*b*) septicemia, and (*c*) chronic nonspecific arthritis of the spine (spondylitis deformans). The hypothesis that the dislocation, when spontaneous, is a distention luxation is supported.

FROM THE AUTHORS' CONCLUSIONS.

THE RÔLE OF AURICULOCARDIOPULMONARY REFLEX IN DEATH FROM DROWNING. E. FROMMEL, J. de physiol. et de path. gén. **31**:327, 1933.

Water under pressure in the external auditory canal may cause inhibition of breathing without complete arrest, bradycardia either of sinusal origin or due to auriculoventricular dissociation, and increase in systolic and fall in diastolic pressure. These phenomena are in all respects comparable to those that result from the irritation of the nasal mucous membrane by water; they belong in the group of the inhibitory reflexes of the trigeminus and vagus. The reflex is regarded as explaining certain deaths of persons while swimming.

RUPTURE OF ALVEOLAR ECHINOCOCCUS CYST INTO THE PERITONEAL CAVITY AS A CAUSE OF SUDDEN DEATH. W. NEUGEBAUER, Centralbl. f. allg. Path. u. path. Anat. **58**:228, 1933.

A woman, 33 years of age, who had always been healthy, suddenly showed symptoms of peritonitis three days before her death. Abortion was suspected by the medical attendants, but at necropsy 1.5 liters of foul exudate was found in the abdomen. This material had apparently come from a ruptured cavity in the liver, the size of two fists. Rupture occurred into the omental bursa. The case is unusual in that no icterus was present before death. Usually compression of gall capillaries and widespread parenchymal necrosis lead to severe jaundice. There were no splenic enlargement and no enteritis. Echinococcus alveolaris ruptures much less frequently than does the hydatid form, and rupture of either is far more frequent into the subphrenic space or the pleural or pericardial cavity than into the omental bursa.

GEORGE RUKSTINAT.

MICROSCOPIC APPEARANCES OF THE GASTRO-INTESTINAL TRACT IN CHARRED BODIES. E. FRITZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:19, 1934.

Microscopic examination of the gastric and intestinal mucous membrane showed perfect preservation of the surface epithelium with good nuclear staining. This state of preservation indicates that the heat had continued to act for a short time after death. In experiments on animals it was found that, when fixed by heat, mucous membranes resisted decomposition for three months after burial in earth.

FROM THE AUTHOR'S SUMMARY.

EXAMINATION OF THE WEAPON IN SUICIDE BY SHOOTING. BRUNING and WIETHOLD, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:71, 1934.

In shooting with the muzzle against the skin fragments of blood and tissue nearly always enter the barrel, and consequently in doubtful cases examination of the weapon is of great importance.

SUICIDE BY CONSTANT CURRENT OF 220 VOLTS. W. MUNCH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:97, 1934.

Three cases of this rare form of suicide are described in detail, and twenty-nine reports in the literature of suicide by electric current are tabulated. In most cases the arrangement of the wires pointed directly to suicide.

DOUBLE MURDER BY THALLIUM. HERMAN KRSEK, Časop. lék. česk. **73**:40, 1934.

According to Krsek, this is the third report on homicidal thallium poisoning. The material used was Zeliopaste, which contains about 0.68 Gm. of thallium sulphate per tube. It is tasteless and is on unrestricted sale as a rat exterminator. The victims were the matrimonial partners of a middle-aged loving couple. The postmortem observations were practically negative in the man, who had received within a month an amount of thallium sulphate estimated to be between 0.68 and 2.05 Gm. The thallium content of his body was estimated at 1.33 Gm. The

woman's body contained about 1.62 Gm. It was exhumed eight months after death and was markedly better preserved than the average corpse in that cemetery. The lethal dose seems to be between 1 and 2 Gm. The changes which should arouse suspicion of thallium poisoning are clinical rather than pathologic. Thallium was mistaken for arsenic by the chemist in the case described by Kaps and Haberda. Gastro-intestinal symptoms accompanied by polyneuritis affecting especially the lower extremities (marked stabbing pains), hypo-acidity and trophic changes of the skin and especially loss of hair suggest this poisoning. In protracted cases—such as that of a woman who had received four doses in the course of three months—the physical symptoms may be dominated by mental disturbances of a hysterical or delirious character.

KAMIL SCHULHOF.

THE AIR CONTENT OF LUNG TISSUE. E. HUSTED and A. SAUGMAN, Acta path. et microbiol. Scandinav. **11**:227, 1934.

The authors have devised a modified floating test whereby the lung tissue is placed in water in a sealed container connected with a manometer and by a three-way stopcock with apparatus for increasing and decreasing atmospheric pressure. By means of a mathematical formula and a table it is possible to determine the percentage of air in a given piece of lung tissue. The authors tested fifty-three specimens of lung tissue from twenty-three persons, including fifteen newly born. Normal fully expanded lung could not be made to sink in the water. The air of the lungs has to be reduced considerably before an overpressure of from 500 to 600 mm. is able to sink the tissue. A partly atelectatic piece of lung from a newborn infant who died fourteen hours post partum sank in the ordinary floating test, but could be made to rise with a pressure of —130 mm. By this simple test it is possible to demonstrate the presence of air in lung tissues when the ordinary floating test shows apparently air-free lungs.

JACOB KLEIN.

EXPERIENCES WITH FATAL HEAD INJURIES. F. HARBITZ, Norsk mag. f. lægevidensk. **95**:353, 1934.

Harbitz studied 115 fatal head injuries of which 50 were homicidal, 40 accidental and frequently associated with drunkenness and 25 due to automobile injuries. He has a detailed tabulation of 20 cases in which in addition to skull fracture there were hemorrhage between the brain coverings, tearing of the brain cortex and hemorrhage of the brain in the central ganglions, pons and medulla oblongata. These injuries were especially common after automobile accidents, and most marked in the temporal region. In 83 bodies there were: large epidural hematomas in 13, either with or without a skull fracture; extensive subdural hemorrhages in 19; large hemorrhages in the arachnoid in 14; tears and hemorrhages of the brain cortex, and in 12, small hemorrhages in the interior of the brain, mostly in the line of direction of the acting force. Harbitz reports five deaths from commotio cerebri. He found no constant anatomic alterations in this condition. He is of the opinion that there is no sharp boundary between commotio cerebri and contusio cerebri and does not believe the cause of the former or the reason for its causing death is established. He has not seen hemorrhage in the interior of the brain in the central ganglions or pons or medulla, with breaking into the third or fourth ventricles due to violence to the head, in the absence of skull fracture, hemorrhage into the brain coverings or tearing of the brain cortex with some small outer damage. Three cases of combined traumatic and spontaneous bleeding in the brain were encountered in men from 53 to 61 years old. The hemorrhages regarded as spontaneous were situated in the pons. He warns against drawing conclusions in such cases because emphasis on the traumatic features may have widespread medicolegal implications. Two deaths in men known to have hypertension, but who had injuries to the face as well as intracerebral hemorrhages, were regarded as due to natural causes. It was assumed they had the intracerebral lesion first and then fell, injuring the face.

GEORGE RUKSTINAT.

Society Transactions

BUFFALO PATHOLOGICAL SOCIETY

Regular Meeting, May 12, 1934

KORNEL TERPLAN, *President, in the Chair*

ACUTE LEUKEMIC RETICULO-ENDOTHELIOSIS. JOHN LOESCH.

Five weeks prior to his admission to the hospital a white man, aged 30 years, an iron-worker in an automobile factory, noted the development of hemorrhagic areas in the skin over the entire body. Three days later his throat became severely sore and his neck swollen. Following the appearance of these conditions, which grew progressively worse, jaundice was noticed; bleeding from the mouth and rectum occurred. Exposure for thirty-six hours on an ice flow in Lake Erie antedated the patient's illness.

On physical examination the skin, in addition to the hemorrhagic lesions, showed, especially on the chest and abdomen, circular elevated nodules of sizes up to that of a dime. The liver projected four fingerbreadths below the costal margin. The spleen reached into the pelvis. The inguinal nodes were enlarged. The laboratory work showed: erythrocytes, 2,580,000, and leukocytes, 12,200, per cubic millimeter, with adult polymorphonuclears 3 per cent, lymphocytes 27 per cent and monocytes 69 per cent. In the last group, the nuclei were round or elliptic in 28 per cent, slightly indented in 23 per cent, deeply indented in 10 per cent and lobulated in 8 per cent. Mitotic figures were noted. Frequently the cytoplasm of the monocytes contained fragments of red blood cells. The blood platelets appeared diminished in number. The bleeding time was fifteen minutes; the clotting time, twenty minutes. A blood culture was positive for hemolytic staphylococcus. The clinical diagnosis was: acute leukemia and septicemia with multiple abscesses.

The chief postmortem observations comprised: marked jaundice; multiple hemorrhages and circular elevated nodules in the skin; petechial hemorrhages of the uterus and serous membranes; marked enlargement of the liver; marked enlargement of the spleen; enlargement of all the lymph nodes, especially those in the left tracheobronchial and inguinal groups; numerous white areas, 0.5 cm. in diameter, scattered throughout the myocardium, papillary muscles and kidneys; 250 cc. of slightly hemorrhagic fluid in the peritoneal cavity, and yellowish-red bone marrow.

Histologic examination of the liver, spleen, various lymph nodes, skin bone marrow, kidney, myocardium and tonsil, showed a uniform proliferation of large mononuclear cells with abundant cytoplasm and very often with distinctly indented nuclei. The picture, especially in the myocardium, resembled closely a blastomatous infiltration. Pathologically, this condition, the intravital blood picture of which corresponded to a so-called monocytic leukemia, was diagnosed as acute leukemic reticulo-endotheliosis. The history of exposure was considered in a discussion of the etiology.

DISCUSSION

K. TERPLAN: This case evoked considerable discussion in the matter of differential diagnosis, but from a histologic analysis of Dr. Loesch's slides I feel that an acute myeloblastic leukemia can be ruled out. The nuclei of the cells shown possess a structure that is generally recognized as belonging to those of reticulum cells or monocytes. I am especially impressed by the blastoma-like infiltration of the myocardium. Dr. Loesch's case is certainly different from the instances

reported in the literature as acute reticulo-endotheliosis, in which no increase of monocytes was noted in the circulating blood. In these cases the histologic picture also resembled that of a reactive hyperplasia of reticulum and endothelial cells. In some, the unusual reaction was explained on the basis of an infection.

ACUTE LEUKEMIA FOLLOWING ADMINISTRATION OF ARSPHENAMINE. S. L. VAUGHAN, K. TERPLAN AND S. SANES.

Cases of acute apparently lymphatic leukemia following arsphenamine therapy are relatively rare.

A white man, aged 54 years, was admitted to the Buffalo General Hospital, complaining of a swelling on the left side of the face of five days' duration. He had finished an intensive course of sulpharsphenamine injections for tertiary syphilis three months previously. Physical examination revealed swelling of the parotid gland resembling acute parotitis, primary optic atrophy and palpable inguinal lymph nodes. The liver and spleen were not felt. The temperature was 100.6 F. The urine contained 0.01 mg. of arsenic per hundred cubic centimeters.

The blood revealed 2,200,000 erythrocytes per cubic millimeter, of uniformly large size, predominately oval shape and even staining. Reticulocytes were 0.2 per cent. The hemoglobin content was 56 per cent. The leukocyte count was 2,200 with 2 per cent filament neutrophils, 1 per cent eosinophils, 84 per cent lymphocytes and 13 per cent monocytes. The thrombocyte count was 123,000, the Wassermann reaction 4 plus.

On intramuscular injection of liver extract there were a rise in the total leukocyte count to 4,700 and a fall in the thrombocyte count to 86,000, but no significant changes in the erythrocyte or differential counts.

Five daily injections of pentose nucleotide were followed by further rise in the leukocyte count to 5,900, due to the appearance of cells regarded as young monocytes in the concentration of 19 per cent. The peroxidase reaction on these cells was negative. The erythrocytes showed polychromatophilia and poikilocytosis for the first time.

After an afebrile period of two weeks the temperature began to rise again and remained elevated thereafter. Exudate which was obtained from a few pustules that had developed on arms and face was quite fluid, and contained very few polymorphonuclear cells. The predominating cells closely resembled those seen in the blood, although many of them gave a strongly positive peroxidase reaction. Staphylococcus aureus was recovered in pure culture.

During the next month the leukocyte count rose to 55,000, and after a temporary fall, to 124,000. Polymorphonuclear cells remained less than 1 per cent, lymphocytes 30 per cent, mature monocytes 9 per cent, and the cells described previously 60 per cent. In the terminal stage the last cells became less granular, but a small percentage of them gave a positive peroxidase reaction. The anemia progressed slightly, and a thrombocytopenia of 25,000 developed. An ulcer appeared on the gum. Lymph nodes became palpable for the first time in the neck and axillae. Death occurred ninety-four days after admission.

Autopsy showed: marked generalized anemia; distinct hemosiderosis of the liver; marked "tigering" of the heart, with dilatation; minute whitish infiltrates scattered regularly throughout the cut surface of the liver, which was not conspicuously enlarged; enlargement of the spleen (weight, 280 Gm.), with entirely obscured structures; anemic jelly-like appearing bone marrow in the spine and the sternum; fatty marrow in the femur; moderate turgescence of the penis suggesting priapism; moderate enlargement of the peripancreatic, periaortic, pelvic and inguinal lymph nodes; distinct yellowish-white clots in the large veins and heart; rather watery blood issuing from cut vessels.

Histologically, the spleen, liver, lymph nodes, kidneys, corpora cavernosa, heart muscle and bone marrow exhibited a uniform proliferation chiefly of immature large round cells which were considered as lymphoid elements including lymphoblasts. The distribution of the infiltration in the liver and kidney pointed to lymphatic leukemia. Practically not one of the cells showed granular cytoplasm.

There was no proliferation of reticulum cells. No recognizable myeloid elements were noted.

Whether the true leukemic stage is a compensatory effort to a marked suppression of bone marrow, or whether it represents a direct response to the toxic agent, sulpharsphenamine, can hardly be decided in the case here reported.

PRIMARY CARCINOMA OF THE STOMACH—GROSSLY UNRECOGNIZABLE—WITH EXTENSIVE METASTASES TO THE BONE MARROW PRODUCING MARKED INTRAVITAL ERYTHROBLASTOSIS. K. TERPLAN AND S. L. VAUGHAN.

This case is presented because the results of clinical and hematologic examinations were rather suggestive of a malignant process of the gastro-intestinal tract with metastases to various parts of the bone marrow. Yet gross inspection at autopsy failed to disclose clearly the site of the primary tumor.

A Polish woman, 42 years of age, was admitted to the General Hospital, Jan. 31, 1934, complaining of weakness and loss of 62 pounds (28.1 Kg.) in weight for one year. For three months prior to her entry the patient suffered with anorexia and generalized body pains.

Physical examination revealed an emaciated cachectic patient, with marked general pallor and with an indistinct yellowish cast to the skin and conjunctiva. Lymph nodes not exceeding the size of a pea were palpated in the neck, axillae and groin. The heart was enlarged to the left; a systolic murmur was heard over the apex and the base. The liver extended from the seventh interspace to the level of the umbilicus in the anterior axillary line. It was tender. The spleen reached to the level of the umbilicus. A moderate amount of fluid was in the peritoneal cavity. A number of lentil-sized discrete nodules were felt on the right pelvic wall by rectal examination.

A colonic injection showed no evidence of neoplasm. The urine contained abnormally large amounts of urobilinogen. The gastric contents were negative for hydrochloric acid after injection of histamine. Evidences of pyloric obstruction were not found. The feces were negative for occult blood on two occasions; the color was dark brown. The blood serum contained 1.4 van den Bergh units of bilirubin. The red blood count was 1,700,000; the hemoglobin content was 44 per cent. The cells varied considerably in size with the average distinctly greater than normal. Poikilocytosis and polychromatophilia were marked. Staining was normally intense; stippling was present. Erythroblasts numbered 6,200 per cubic millimeter. Of the erythrocytes, 17 per cent were reticulated. The leukocytes numbered 8,700 per cubic millimeter, with myelocytes 18 per cent, juvenile forms 14 per cent, band forms 27 per cent, filament forms 15 per cent, eosinophils 1 per cent, lymphocytes 16 per cent; lymphoblasts 2 per cent, monocytes 6 per cent and Türck's cells 1 per cent. The thrombocytes, many of which were dime-sized, numbered 30,000. The clinical picture suggested malignant tumor, probably in the gastro-intestinal tract. The profound anemia with thrombocytopenia accompanied by a tremendous regenerative effort in both the erythrocytic and white cell series was thought to be diagnostic of sudden extensive encroachment on active bone marrow tissue, such as one might expect from tumor metastases.

At autopsy there were marked generalized marasmus and anemia. The stomach appeared distinctly contracted. It showed slightly increased mucoid secretion and rather prominent folds. The mucosa was entirely intact. Grossly, infiltration at any part of the wall of the stomach could not be noticed. Only at the upper part of the lesser curvature were the serosa and mesogastrium firm and thickened. There were also a few small slightly cystic nodules in the omentum and rather many minute metastases in the lungs and bronchomediastinal lymph nodes. Both ovaries were moderately enlarged. The vertebral bodies, especially those of the lumbar spine, were diffusely invaded by soft metastatic tumor. The histologic type was adenocarcinoma, with marked mucoid production. Sections taken from different parts of the stomach revealed that the primary tumor originated apparently in the upper part of the fundus near the lesser curvature. The superficial layer of mucosa was intact. There was a slight disorder of the

glands in the depth of the mucosa with distinct infiltration of the lymph spaces. The submucous spaces were entirely filled with carcinomatous cells. Here and there the carcinomatous cell cords extended through the muscularis mucosae. Diffuse invasion also was seen in the muscle layer and subserous spaces, even in areas more distant from the lesser curvature. Metastases from the omentum, lung and bronchomediastinal lymph nodes showed the same histologic type throughout; the ovaries showed the typical picture of so-called Krukenberg tumor. The liver and spleen exhibited unusually marked myeloid metaplasia; the histologic observations were hardly different from those seen in true myelogenous leukemia.

This is the second case in which, so far as we know, primary carcinoma of the stomach produced no structural alteration of the entire stomach which could be grossly detected. The first case was reported several years ago from Prague by one of us (Terplan, K.: *Beitr. path. Anat. u. z. allg. Path.* **87**:229, 1931).

STUDIES OF BLOOD CALCIUM, POTASSIUM AND CHOLESTEROL IN DOGS FOLLOWING KIDNEY DAMAGE, EXPERIMENTALLY PRODUCED. JOHN LOESCH.

Series A.—In dogs on a standard diet the kidney was damaged by ischemia. This was accomplished by clamping the renal pedicle for a certain duration at certain intervals. The calcium figures were normal except in the terminal stage, when the changes were not consistent. In some animals the values decreased, occasionally to 50 per cent of the initial ones. In other animals the figures were increased. The potassium, however, was uniformly elevated and reached highest values in the terminal stage. The potassium-calcium quotient rose simultaneously with the foregoing changes.

Series B.—In dogs on a standard diet as much as three fourths of the total renal parenchyma was removed. No significant changes occurred in potassium, calcium or the potassium-calcium quotient. When the protein in the diet was increased, the potassium always tended to rise, and the highest figures were found in the uremic stage. As the calcium remained normal or decreased slightly, the potassium-calcium quotient increased.

In an attempt to establish a relationship in each series between calcium, potassium and the potassium-calcium quotient on the one hand and the nonprotein nitrogen, plasma protein content and plasma percentage on the other hand, it was found that of the first three the potassium and potassium-calcium quotient alone varied in direct proportion to the last three.

As the cholesterol figures showed great variation in both series definite conclusions could not be drawn from them in any of the experiments.

The foregoing work was carried out simultaneously with the studies of plasma proteins reported before the Buffalo Pathological Society, at the meeting of Nov. 14, 1932 (ARCH. PATH. **14**:901, 1932).

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, May 24, 1934

WILLIAM C. VON GLAHN, *President, in the Chair*

MITRAL STENOSIS WITH INTERAURICULAR INSUFFICIENCY. SEATON SAILER (by invitation).

A case of mitral stenosis with interauricular insufficiency is reported in a white man of 67 years. This brings the total number of cases reported to twenty-seven. It is the third reported case occurring in a male. A clinical diagnosis of this combination of lesions is possible, being determined mainly by roentgen and fluoroscopic examination. The criteria are as follows: There is an enlarged,

transverse and sabot-shaped heart. The abnormality is caused by a great enlargement of the right auricle and ventricle with rotation of the left ventricle posteriorly, the right ventricle forming almost the entire anterior aspect of the heart, including its apex. The pulmonary artery is greatly enlarged throughout, and its hilar branches form discrete rounded shadows. The aorta is hypoplastic. Fluoroscopic examination shows an upward and outward counter-clockwise movement of the right ventricle during systole with uncovering of its inferior border, normally hidden in the diaphragm. The hilar shadows of the pulmonary artery show an expansile pulsation. Auscultatory signs of mitral stenosis or of a patent interauricular septum are corroborative, but not constant. The electrocardiogram shows right ventricle preponderance and notched R waves in all leads. The P and T waves show no distinct changes.

In the case which I shall now report the heart weighed 700 Gm. A moderate degree of stenoiss of the mitral valve was present. It measured 9 cm. in circumference. The right ventricle measured 1.5 to 1.7 cm. in thickness. The pulmonary artery was symmetrically enlarged, measuring 11.5 cm. in circumference to its point of bifurcation. Its ramifications throughout the lung were greatly enlarged. The aorta measured 6.5 cm. in circumference. Microscopically both vessels showed slight degenerative changes of the medial muscle cells and fraying of the elastic tissue. A defect 3 cm. in diameter was present at the lower border of the auricular septum above the septal flap of the tricuspid valve, the endocardial lining of this valve being continuous through the foramen with that of the posterior mitral curtain. The right auricle was markedly dilated and hypertrophied; the left, moderately involved. A slight fusion of the commissures of the aortic valve was present, with resulting hypertrophy of the wall of the left ventricle. Death was caused by confluent bronchopneumonia involving the middle and lower lobes of the right lung and the lower lobe of the left lung.

SYNOVIOMA: A REPORT OF THREE CASES. LEILA CHARLTON KNOX.

Under the name "synovioma" may be designated a special group of malignant connective tissue tumors occurring in the extremities and arising from the synovia of joints, tendon sheaths and bursae. These may be either intra-articular or extra-articular. The intra-articular group are apparently more slowly growing and inclined to be nodular for a longer period of time, but like those external to the joints, they recur and frequently metastasize widely. These growths have been most extensively described by the French school.

Three cases are presented. The first occurred in a young woman, the tumor arising from either a bursa or a tendon sheath on the ulnar aspect of the right elbow. It caused pain for one and a half years, and then grew fairly rapidly for another year and a half. Amputation was done in August 1921. The patient remained in good health for over six years, but died with extensive recurrences in the shoulder, chest and cervical nodes in 1928.

The second patient was a man 33 years of age, first seen in June 1929, with a tumor in the right popliteal space, which had originated apparently around the tendon sheaths and had grown slowly for six months until it was removed locally for microscopic examination. A midthigh amputation was done a few days later, but the patient died early in 1932, with roentgen and clinical evidence of metastatic tumor of the right lung.

The third patient is a man 24 years of age who had a tumor on the plantar surface of his left foot which had been causing pain and disability for two and a half years. The growth was found under the plantar fascia and surrounding the tendons. It was infiltrating diffusely, and was operated on. The first diagnosis was hemangioma. A diagnosis of malignant tumor was made microscopically, and the leg was amputated three weeks later. The patient is now, two years after the operation, without clinical evidence of metastasis.

The microscopic appearance of these tumors is that of a small spindle-cell sarcoma with a tendency toward mucinous degeneration of the cytoplasm. The

nuclei are not extremely hyperchromatic, but the number of nuclei in any field is large. A characteristic feature not present in every section, but probably present in every tumor, is the organoid structures superficially resembling epithelium in which the altered fibroblasts tend to surround a lumen, although no basement membrane, epithelial secretions or cilia are found. These structures probably represent the tendency of the tumor to reproduce in some of its cells the alterations that take place when a synovial membrane forms about a free cavity.

Except for the presence of these pseudoglandular structures, the tumors closely resemble some types of periosteal sarcoma, from which they should be differentiated. Roentgenograms of the bones show no involvement in the early stages, and only pressure atrophy and absorption or secondary invasion in the late stages.

They should also be differentiated from xanthomas of the tendon sheaths, frequently designated as giant-cell sarcoma, the xanthomas being benign growths, never malignant. The effects of radiation on the tumors have not been established, as so few of them have been recognized and treated with measured quantities for any adequate period. Amputation is frequently necessary, but undoubtedly some patients have been cured with less radical treatment.

DISCUSSION

ALFRED PLAUT: How do such tumors react to radiation? I should like to ask also about the clear substance of some of the cells: Does it give any metachromatic reaction with mucicarmine or thionine?

FRANCIS CARTER WOOD: I have been following for a number of years a patient with a tumor of the popliteal space probably belonging in this group though it was purely spindle cell in type. The sections were not very good, and I have doubted the clinical diagnosis somewhat because the patient is still alive. But it has been only five years since his operation, so that one still has a chance to prove or disprove the presence of malignancy. There was none of the alveolar structures that Dr. Knox's tumors showed. The growth was very radically removed and then the involved region was heavily irradiated, with rather disastrous results, for when I saw the patient, he was suffering more from his irradiation than from his tumor. He had a large ulcer over the popliteral space where the radiation had been applied, and there was some question of further surgical intervention, which I opposed. I saw him a few weeks ago, and he was in perfect health; the ulcer had finally healed. His was a very puzzling case; the slides were shown to a number of pathologists, and a great variety of diagnoses were made.

It is important that Dr. Knox has given a picture of this condition so that cases can be recognized promptly. I should not think the growths would be radiosensitive, any more than the other spindle-cell sarcomas are. One has to differentiate tumors of this type clinically very carefully from the other group of tendon sheath tumors, that is, the giant-cell tumors, which are merely inflammatory reaction products; in the older literature the latter type is often confused with tumors of the type just described, so that the older pathologists thought they might be melanoma. That group of tendon sheath tumors never evinces malignancy, though they may recur locally.

LEILA CHARLTON KNOX: Very little has been learned from special stains. There is no mucoid secretion, nor any metachromic reaction with the mucicarmine stain. The eosin and hematoxylin stains show better than others the relation of the cells to one another.

With regard to radiosensitivity there are very few observations, because the total number of treated persons is so few, and the technic of radiotherapy has been altered so many times in the last ten years that even the few observations which have been made may not be significant for the group. Smith (*Am. J. Path.* **3**:355, 1927) cites two cases in which such treatment was given, and the cutaneous and pulmonary metastases were very considerably improved by the x-rays. That was only a few years ago. One of Dr. Wagner's patients, the one with the large intra-articular tumor, was treated by Dr. Wood for some time before he

consented to have his leg amputated, and during that time the tumor was slowly growing into the head of the tibia. Therefore that particular tumor was not radiosensitive. In the second case that I cited the metastases in the chest were treated with radiotherapy. The patient showed no improvement. That may have been because the tumor was rather extensive at the time treatment was begun, but tumors of this type are certainly not highly sensitive to radiation.

ALFRED PLAUT: I suppose it is possible by x-ray picture to make a correct differential diagnosis between a bone sarcoma on which one would not do a biopsy, and a tumor such as this, in which one would like to have a biopsy first, in order to decide on amputation.

LEILA C. KNOX: The question probably has to be settled by biopsy. There was some erosion of both condyles of the femur in one patient and of the heads of the humerus and radius in another of these patients, but it seemed to be purely secondary. The tumor was invading the bone as it invaded the soft tissues, and the outer part of the cortex was gone. But the shaft of the bone was still there. The large intra-articular tumor usually makes a cavity for itself. In many of the cases the growth has clinically resembled tuberculosis of the joint. The older French and German literature discloses that many of the patients were believed to have tuberculosis of the joint because of the spindle-shaped swelling and the semi-fluctuation.

HIRSUTISM, HYPERTENSION AND OBESITY ASSOCIATED WITH CARCINOMA OF THE SUPRARENAL CORTEX AND AN INDETERMINATE PITUITARY ADENOMA. IRVING GRAEF and (by invitation) ANTONIO ROTTINO and JOSEPH J. BUNIM.

The case of a patient exhibiting the symptoms of hypertrichosis, rapidly acquired obesity and hypertension is presented: H. B., an unmarried white woman of 19 years, was studied on the Third (New York University) Medical Service of Bellevue Hospital from Nov. 13, 1933, until death, Jan. 31, 1934. The complaints were of progressive weakness and edema of the feet of nine months' duration.

The onset of menstruation was at 12; the flow recurred every thirty days and was painless and moderate, lasting seven days. There were no menses during March or April of 1933 or during the last two months of her life.

The hypertrichosis was sufficiently marked to require shaving of the face in the last four months.

In November 1933 the blood pressure was 124 systolic and 90 diastolic; subsequently the systolic pressure ranged from 168 to 180, and the diastolic, from 125 to 138.

The patient was of hypersthenic habitus, weighed 156½ pounds (71 Kg.) and measured 65 inches (165 cm.). The body had a peculiar pungent, sweaty odor.

Long, broad striae were seen over the abdomen and upper part of the thighs; smaller ones over both mammae and the upper part of the arms.

Hypertrichosis consisting of tawny yellow hair was noted over the face, upper lip and both extremities. There was female distribution of the pubic hair. The clitoris was of normal size. There was marked edema of both legs.

No voice changes were noted. The Aschheim-Zondek test was negative. The basal metabolic rate was —7 and +3 per cent. The Wassermann test was negative. Urinalyses showed proteinuria (from + to ++++). The specific gravity ranged from 1.005 to 1.015. No reducing or acetone bodies were detected. Dextrose tolerance was diminished. Roentgen study of the chest showed several circumscribed areas of increased density in both pulmonary fields, suggesting metastatic new growths.

Dr. Robert T. Frank of Mount Sinai Hospital made hormonal studies of the patient's blood and urine. He reported: "The urine contained 5,000 mouse units of female sex hormone per liter; as a control, the Friedman test was done with the same urine on two rabbits, with negative results. There was no excess of anterior pituitary-like factor in the urine. The venous blood contained 1 mouse unit in 40 cc., which is a quite normal finding."

Six days before death, the temperature rose to 103 F., and a large abscess was noted in the upper part of the left thigh, from which hemolytic streptococci were isolated. The striae of the lower part of the abdomen began to suppurate, and the patient died in coma.

Autopsy was performed two hours after death. The external examination conformed to the description given. The essential pathologic observations follow: The right kidney was found displaced downward by a large tumor situated at its upper pole. Posteriorly the tumor completely compressed the inferior vena cava and was firmly attached to the right lobe of the liver. Section showed an irregular lobulated appearance. Some areas were butter-yellow; some, the seat of recent and old hemorrhage. There was deep invasion of the right lobe of the liver. The inferior vena cava from its opening in the right auricle was filled with soft tumor deposits.

In the lungs were numerous metastatic nodules. The heart was not enlarged; the wall of the left ventricle was of normal thickness. The left suprarenal gland was small and wrinkled. Both ovaries were small and firm. Other organs did not show gross changes. On dissection of the pituitary body no gross changes were found. It measured 13 mm. in the anteroposterior lateral, 14 mm. in the lateral, and 6 mm. in the vertical, plane.

Microscopic sections of the tumor revealed a new growth consistent with the observations in carcinoma arising in the cortex of the suprarenal gland. Tissue fixed in absolute alcohol and stained by Best's method showed no glycogen. The thyroid gland appeared to be in a resting stage. Both ovaries were relatively bloodless and showed an unusual amount of progressive atresia of the follicles in all stages. Sections of the endometrium showed atrophy of the glands and marked edema of the outer two thirds of the mucosa. In the left suprarenal gland the medulla appeared scanty, the cortex narrow and the zona reticularis atrophic. The pineal body showed no changes. The other organs with the exception of the pituitary gland were not significantly altered. After fixation in Zenker's fluid the halves of the pituitary body were embedded in paraffin.

Serial sections of the pituitary body, 5 microns thick, were prepared. In one block a circumscribed miliary nodule was found, which was oval-shaped and measured 1 mm. by 850 microns. At first, from hematoxylin and eosin sections alone it was thought that this was a basophilic adenoma, but special cytoplasmic stains, such as Sevringhaus' method, Bailey's method employing acid violet and Altmann's aniline fuchsin, Mallory's aniline blue, the Weigert method employing gentian violet, iron hematoxylin, Heidenhain's azo-carmine, and a new method introduced by Soas and Csizek, revealed features as follows: There were a few eosinophils and an occasional intact basophil in the periphery of the nodule, but the vast majority of the cells showed an ill-defined cytoplasm in which no chromophilic granules were demonstrable. While the majority of the cells tended to take a feeble purplish tone with hematoxylin, ordinary immersion in 1 per cent aqueous eosin for one minute gave them a reddish tint. Reticulum stains (the method of Foot and Foot) revealed the absence of the normal reticular stroma within the nodule and a poorly defined capsule which demarcated the nodule clearly from the adjacent tissue. The configuration of the adjacent tissue showed compression of the cords of the nodule.

The nature of this nodule was difficult to determine; it partially satisfied the criteria given by Kraus in his study of anterior pituitary adenomas. It possessed a capsule and compressed the adjacent tissue, and for the most part it was composed of chromophobic cells, degenerating and poorly defined. The state of these cells was unusual. Many multinucleated forms were seen, and while the eosinophils were well preserved, the cells here as well as the occasional basophils at the periphery showed profound cytoplasmic and nuclear changes.

These changes were not confined to the nodule, however, and were seen in the basophils elsewhere in the pars distalis. These consisted of marked nuclear swelling, dissolution, vesiculation, lobulation, amitotic division, extrusion of nucleoli, wrinkling of the nuclear membrane and the cytoplasmic membrane, and loss of

cytoplasmic granules. The eosinophils remained well preserved. The sections of the pars nervosa showed no invasion of epithelial elements, and the pars tuberalis also seemed normal.

Interpretation of these observations in the light of present knowledge is difficult. Pituitary disorders are known to influence the suprarenal cortex; for example, aplasia of the cortex in anencephaly, P. E. Smith's experimental atrophy of the suprarenal cortex in hypophysectomized rats and cortical adenomatosis of the suprarenal gland in Putnam's dog rendered acromegalic by injections of anterior pituitary extract. There is clinical evidence of the suprarenal-pituitary relationship in acromegaly and in infantilism. Of great interest are the eighteen cases of pituitary basophilism (Cushing) now recorded. Nine of the patients showed cortical hyperplasia or hypertrophy of the suprarenal gland and one an adenoma of the suprarenal cortex.

While the pituitary adenoma in the present case may have been a coincidental finding, to decide this even tentatively is difficult. It is pointed out that there are no satisfactory statistical data on the incidence of pituitary adenomas in the general population independent of pituitary disorders. A synthetic series based on Erdheim's, Kraus' and Kiyono's serially sectioned pituitary glands shows that adenomas are rare in youth. Evidence to show more than a coincidental relationship between the suprarenal and the pituitary gland in this case is submitted from the literature: 1. A case reported by Oppenheimer and Fishberg (*Arch. Int. Med.* **34**:631, 1924) of a man of 24 with a suprarenal cortical tumor and hypertension. The authors noted that their patient had an acromegalic appearance. 2. A case reported by Long and Gray in the *Medical Journal and Record* (**119**:38, 1924) of a metastasizing suprarenal cortical carcinoma in a man, aged 45, in whom an acromegalic appearance developed while he was under observation. In the first case no statement was made concerning histologic examination of the pituitary gland. In Long and Gray's case, casual sections were reported to show an overgrowth of eosinophilic and chromophobic cells, also epithelial cell invasion of the pars nervosa. 3. A case reported by Mathias (*Virchows Arch. f. path. Anat.* **236**:446, 1922) of an 18 year old girl with hypertrichosis since the age of 3 who died with a metastasizing suprarenal cortical neoplasm. Serial sections revealed a marked increase of eosinophilic elements and, further, an overgrowth of the chief cells which in one place had the character of an adenoma.

If, as Cushing has shown, tumors of the pituitary gland are frequently associated with hyperplasia of the suprarenal cortex, it is suggested that the evidence presented from the literature, as well as in our own case, tends to show that tumors of the suprarenal cortex may be associated with changes or manifestations of changes in the pituitary body.

DISCUSSION

ROBERT T. FRANK: I am thankful for the chance to see this patient during life, and later, after death, to obtain enough of the organs to make extracts, because I had a similar case which I studied for over a year and a half. Without taking any position in the discussion of whether this is of primary basophilic or of suprarenal origin, I may say that the syndrome is very striking. The case I had will be reported in detail by Dr. Oppenheimer and myself; the patient died on Dr. Oppenheimer's service, but I am particularly interested in showing some of the biologic changes which have taken place.

The patient had the typical appearances of what Cushing described as basophilic adenoma: hirsutism, particularly noticeable on the chest and face; a pendulous abdomen, and small legs and arms in contrast to the thick, fleshy abdomen. The striae were very marked, but not so marked as in the case presented by Dr. Graef. I was so convinced that the patient had a basophilic adenoma that I took occasion at the meeting of the Congress of Surgeons and Physicians in 1933, at which Dr. Cushing was presiding, to present the case as one of basophilic adenoma, and as the first in which the hormones had been studied. This slide shows the female sex hormone in the blood. It is that of the normal female. It also shows the prepituitary secretion in the blood, which likewise shows no abnormality, but the

excretion of the estrogenous substance in the urine was tremendous. This small area shows the amount of female sex hormone which is excreted by a normally fertile menstruating woman during a cycle, while this patient excreted as much as 17,500 mouse units of sex hormone in the course of three days. The ordinary female excretion is about 1,500 mouse units in thirty days. The tremendous excretion led us to make numerous tests for pregnancy, the results of which proved to be negative.

Dr. Bunim asked me how a patient who has atrophic ovaries, as our patient and Dr. Graef's had, with an atrophic endometrium, can produce such a tremendous amount of female sex hormone that it is split over through the kidneys and exceeds that found in pregnancy, and I cannot answer that question. The nearest approach to an answer that I can give is a purely hypothetic one, and it is permitted to me through the study of the extracts. The tumor itself on extraction gave twice as much female sex hormone to the gram as indifferent tissues such as the spleen, of which I likewise had material. The difference is not tremendously striking. Implantation gave no definite results. This is the hypothesis: The suprarenal gland can produce estrogenic substances under these conditions. The mere fact that this large tumor was comparatively poor in estrogenic substance, though much richer than the other organs, does not necessarily mean that this hypothesis is wrong, because if one takes a portion of a corpus luteum one gets very little female sex hormone there, although one knows that it excretes it in large amount; in other words, it does not correspond to the thyroid gland, which is a storage organ, but to an organ which is in very close relation to the capillaries, and there is an immediate distribution of its product. I put this as an open question, because I have no proof of it. Do the carcinomas and the adenomas of the suprarenal glands differ? Through the kindness of Dr. Wilder and Dr. Snell of the Mayo Clinic I was able to obtain some urine from two persons with adenoma, nonmalignant, who were successfully operated on a year ago at that clinic. All their symptoms have receded since operation, and the results of the tests for hormone were negative, so that the question remains unsettled.

From a diagnostic standpoint this overexcretion may be of extreme importance. X-ray pictures of the sella turcica yield no evidence. The pituitary adenomas are so small that they do not change the bone. On the other hand, if one finds overexcretion in the urine, that may be a test, and I have offered it as a test. An article on the subject has been published in the *Proceedings of the Society of Experimental Biology and Medicine* (**31**:1014, 1934), because such cases are so rare that the profession at large must try it out and see. For example, a thorough study of the urinary tract in our patient showed no displacement of the kidney as in Dr. Graef's patient, although a large carcinoma was found. I have had the opportunity of examining the urine in several cases which resembled cases of the basophilic type, and it has been normal in all of them. I hope, as the test becomes known, that it will be tried by others, and that it will help in differentiation.

ALFRED PLAUT: Dr. Graef gave me an opportunity to study the slides of the hypophysis in his case. About the suprarenal tumor I have nothing to say. Dr. Graef has stressed the fact that little is known about the influence of the suprarenal gland on the hypophysis. In this connection I should like to draw attention to the absence of important hypophyseal changes in Addison's disease. This at least shows that a complete or nearly complete destruction of the suprarenal gland does not necessarily have a morphologic manifestation in the hypophysis.

So far as the hypophysis in Dr. Graef's case is concerned, I should like to divide the question into two parts: first, that of the changes in the cells and the nuclei, second, that of the adenoma. I agree with Dr. Graef that one cannot make any definite statement about the cellular changes. While Dr. Graef was demonstrating his slides it occurred to me that very similar changes had been seen in the hypophysis of a patient with severe endocrine disturbances. This patient also had a large adenoma of the hypophysis. The patient was a pregnant woman, 25 years of age, who died of cerebral hemorrhage during labor. She was very obese; she had had late menarche; she had splanchnomegaly and some changes similar to von Recklinghausen's neurofibromatosis.

In my opinion the adenoma in the anterior lobe of the hypophysis of Dr. Graef's patient is of no importance. Dr. Graef has said that adenomas of the anterior lobe are very frequent. In the hospital with which I am affiliated we went over the last one hundred and ten autopsies in which the hypophysis was removed and found five definite large adenomas. Only four of the one hundred and ten hypophyses were examined in serial sections. In seventy-nine cases only a dozen slides or less were examined. From each of twenty-three hypophyses between twelve and fifty slides were available; in only four cases between fifty and one hundred slides were available. Only one of the five adenomas was found during serial examination. Three of the others were found in hypophyses from each of which little more than a dozen slides were examined. The fifth was detected while fifty slides of the hypophysis were being examined. Our percentage is still much lower than that of Erdheim and of E. J. Kraus. They have found adenomas in 10 per cent of their hypophyses.

Out of our five cases of adenoma only the one that I have mentioned concerned a patient with endocrine disturbance. The other adenomas were found accidentally, one in a woman 67 years old with carcinoma of the kidney, one in a middle-aged man with chronic lymphatic leukemia and lobar pneumonia, one in an old man with coronary sclerosis, and one in a woman 40 years old with metastases from carcinoma of the breast and multiple abscesses of the kidneys.

None of the five adenomas was basophilic. One is easily led into making a diagnosis of basophilic adenoma from a casual examination of the section stained with hematoxylin and eosin. The number of nuclei is often large on account of the small size of the cells; thus the whole adenoma makes a large blue dot in the slide and misleads one into a diagnosis of basophilic adenoma. (Lantern slides were demonstrated.) The adenomatous tissue and the normal tissue of the anterior lobe are continuous in most cases, just as one sees tumor tissue and normal tissue merging into each other in myoma of the uterus, for instance, or in goiter.

In the woman who died of metastases from cancer of the breast, a quarter of the anterior lobe was occupied by an enormous adenoma, which had the histologic appearance described for malignant chromophobic hypophyseal adenoma. Even this tumor did not leave any mark on the habitus of the patient. Little is known about the fate of hypophyseal adenomas. I am able to show you a large adenoma which is almost completely hyalinized and has calcified masses in its center. Only small epithelial trabeculae are left.

Probably, if one made serial sections of the hypophysis as a routine, the percentage of adenomas would increase. So far one know of no clinical effect of these tumors.

Some Observations on the Morphology of Glandular Hyperplasia of the Prostate. Robert A. Moore.

With senility, certain morphologic changes occur in the prostate, apparently independent of any pathologic change. These consist of atrophy of the glands and fibrosis of the stroma. They have been given in greater detail in a previous paper. During this process of senile atrophy several types of hyperplasia may occur. For convenience they made be divided into nonnodular and nodular. In the nonnodular type the glandular hyperplasia may occur in focal areas involving from two to ten acini, or may occur diffusely with involvement of all the acini. The nodular type is the well known hypertrophy of the prostate which involves both the glands and the stroma. It may arise at any point in the prostate, but is most common in the lateral lobes. Many nodules have no relation to the periurethral glands. Morphologically an active and an inactive stage of the hyperplasia may be distinguished. The incidence of the disease increases with increasing age to 75 per cent of all prostates in the ninth decade of life. Carcinoma rarely arises in these nodules of hyperplasia. Experimental studies are now being conducted in an attempt to relate the various types of hyperplasia to the altered morphologic and physiologic state of senility.

Book Reviews

A Textbook of Histology: Functional Significance of Cells and Intercellular Substances. By E. V. Cowdry, Professor of Cytology, Washington University, School of Medicine, St. Louis. Cloth. Price, $5.50. Pp. 503, with 242 illustrations. Philadelphia: Lea & Febiger, 1934.

This book is an interesting departure from the conventional type of textbook of histology with the main emphasis on the detailed description of the microscopic structure of all parts of the body. The principal aim of the book is to build up a clear conception of the relation of minute structure and function in the organs and systems of the body through a well directed study of their constituent cells and elementary tissues. Details that for various reasons are considered as not essential to the immediate purpose have been omitted, e. g., illustrations of what the author calls the obvious, that is, figures showing "at a glance what the actual preparations will lead the students to discover for themselves." But there is no lack of good illustrations and diagrams of facts that are difficult for students to unearth. Many of these illustrations are original, while others are taken from the writings of the author, works on cytology edited by him and from other sources. A commendable feature of the book is the frequent use of tables, twenty-six in all, to present various data such as the nomenclature of the blood cells, the differential properties of the blood vessels, a comparison of the suprarenal cortex and medulla, the characteristics of the constituent parts of the hypophysis and chemical integration by hormonic action. In the latter list commercial names have been omitted almost completely. The effort to avoid undue repetition of the same information in the text, tables and illustrations is another commendable feature that should be copied widely, especially in articles in scientific medical periodicals. Enumeration of the subjects will give a good idea of the general plan and scope of the book: water, the essential vital medium (the body fluids); the blood, the principal integrator; absorptive drainage into the blood (lymphatics and spleen); chemical integration by endocrine products in the blood stream (ductless glands); intake of water, nutriment, accessory food factors and removal of waste (the digestive system); oxygen consumption and carbon dioxide elimination (respiratory system); regulation of constitution of blood and removal of waste (urinary system); rapid neural integration of response to internal and external stimuli (nervous system, sense organs); architectural support (connective system); movement (muscular system); perpetuation of the race (reproductive systems), and unification, protection and adjustment (skin). At the end of each chapter is a clear, concrete summary of the contents as illustrated by that on the spleen: "The spleen is the largest lymphoid organ in the body, but it contains no special cells not found elsewhere and hence can be removed without fatal results. In it the myriads of lymphocytes are not confined in vessels or nodes of their own, as in the lymphatic system proper; nor do they invade an epithelial rudiment, as in the thymus; but they meet the fluids and cells of the blood in the tissue fluid. To facilitate this unique association the walls of the capillaries and venules are made very thin and may even have openings. The circulation is so sluggish that the spleen is supplied with penetrating bands of smooth muscle, the shortening of which presses the blood onward. The chances for absorption by lymphocytes, exposed reticular cells of the connective tissue framework and vascular endothelial cells of substances in the blood stream are excellent. The spleen is indeed a great blood filter and the headquarters of the reticulo-endothelial system. The latter disposes of many sorts of particulate matter, including broken down red cells, and plays an important rôle in some immunological reactions. The spleen is also a blood reservoir capable by contraction of adding materially to the circulating blood. In response to special demands it may revert to its embryonic habit of

forming blood cells." At the end are a valuable bibliography and an index of the authors cited in the text. The style is clear, direct and vivid. Any tendency to rambling or prolixity is checked at once. The book meets admirably the goal held in view by its author "that the students shall gradually visualize more and more accurately the wonderful reactivity of the minute structure of the human body in terms of biochemistry, physiology and pathology and, finally, in practice shall institute measures of assistance with due caution." It will be welcomed by all who are interested in following the growth of knowledge of human microscopic structure in relation to function.

Physiology in Health and Disease. By Carl J. Wiggers, M.D., Professor of Physiology in Western Reserve University School of Medicine, Cleveland. Price, $9. Pp. 1184, with 182 engravings. Philadelphia: Lea & Febiger, 1934.

This book was written to meet the needs of earnest students of medicine both before and after graduation from medical school. The author became impressed with the need of correlating his teachings as a physiologist as closely as possible with the efforts of his clinical colleagues to understand functional disturbances in disease. He found himself hampered in meeting this need in a practical way by the lack of a suitable textbook in which the essentials of physiology in health and disease are presented in suitable form. Herein lies the reason for this book. It is divided into ten sections in which the following subjects are treated: physiology of movement; the physiology of the peripheral and central nervous systems; the coordination of visceral function; the blood and blood-forming organs; respiration; the heart and circulation; the physiology of the alimentary tract; water transport and the excretory systems; metabolism and nutrition, and the endocrine organs and reproduction. The main subdivisions under each section are presented in separate short chapters, an arrangement of advantage for the casual reader as well as for supplementary study in connection with conferences and lectures, as the sequence of chapters may be changed as desired. At the end of each chapter is a selected list of appropriate monographs and reviews, while footnotes give references to articles, mostly recent, on particular topics. The book contains in well organized and well written form a wealth of information of the greatest importance to the study and understanding of physiology in its fundamental relations to modern clinical medicine. The author has rendered a great service to medical study.

Pathologie und Klinik der Granulosazelltumoren. By Dr. Walter Schiller, Assistent der II. Universitäts-Frauenklinik (Prof. Dr. Wilhelm Weibel), Vienna. Price, 16 marks. Pp. 197, with 136 illustrations. Viennia: Wilhelm Maudrich, 1934.

This is a review of granulation cell tumors based on study of original cases and of the literature. After a thorough consideration of the structure, histogenesis and clinical characteristics of the granulation tumors, the author comes to the general conclusion that they arise as primarily benign tumors from undifferentiated remnants of the mesenchymatous nucleus of the ovary. According to the grade of differentiation, they assume immature, trabecular forms or mature, folliculoid forms. In the majority of cases these tumors are unilateral. By the production of hormone they induce endometrial hyperplasia, which before the menopause may result in amenorrhea and eventually metrorrhagia, and after the menopause in irregular bleedings. The possibility of malignant granulation cell tumors must be granted, but it is not possible to separate them with complete certainty from genuine, primary, secondarily solid carcinoma of the ovary. Because the trabecular form of granulation cell tumor is not malignant, there is no justification to treat younger women after removal of such tumors so intensively with the roentgen rays as to produce unneeded castration. The book will interest all who wish to understand fully the granulation cell tumor. Unfortunately, it lacks an adequate index of subjects.

A Practical Treatise on Diseases of the Skin for the Use of Students and Practitioners. By Oliver S. Ormsby, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College, University of Chicago. With revision of the histopathology by Clark Wylie Finnerud, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College, University of Chicago. Fourth edition. Cloth. Price, $11.50. Pp. 1,288, with 622 illustrations. Philadelphia: Lea & Febiger, 1934.

This standard work appears in its fourth edition after thorough revision and with much new material. "Thirty-six new diseases are described, twenty rewritten, and the entire work brought up to date." The literature has been reviewed in an earnest effort to make the book reflect the knowledge of dermatology adequately. The references to its literature are limited largely to articles that contain complete bibliographies. The presentation is clear, concise and orderly. The author is a master in his field and writes under the full sense of his responsibility and authority as a teacher. A phenomenal grasp of the various phases of diseases of the skin is evident on every page. The book is well illustrated, and the pathologist will find the descriptions and illustrations of great help in understanding the structure of cutaneous lesions. The work of the publisher has been done very well.

Books Received

MEDICAL USES OF RADIUM. SUMMARY OF REPORTS FROM RESEARCH CENTRES FOR 1933. Medical Research Council, Special Report Series, No. 197. Price, 9 d. Pp. 40, with 4 illustrations. London: His Majesty's Stationery Office, 1934.

THE INHERITANCE OF RESISTANCE TO BACTERIAL INFECTION IN ANIMAL SPECIES; A REVIEW OF THE PUBLISHED EXPERIMENTAL DATA. A. Bradford Hill. Medical Research Council, Special Report Series, No. 196. Price, 1s. 3d. Pp. 71. London: His Majesty's Stationery Office, 1934.

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